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FAMILIAL BLOOD STUDIES IN CASES OF MEDITERRANEAN (COOLEY'S) ANEMIA

DIAGNOSIS OF THE TRAIT, OR MILD FORM OF THE DISEASE

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NEW YORK

In a previous communication [1] a family was reported on in which both parents and all the children showed stigmas of Mediterranean anemia. Two of the children suffered from the severe form of the disease, while the blood of the parents and of the remaining child, all asymptomatic, revealed distinctive abnormalities of erythrocytes. The occurrence of unquestionable Mediterranean anemia in 2 members of one family and of disturbed erythropoiesis in the others lent weight to the hypothesis that the condition in the cases originally described by Cooley and his associates represented a severe and often fatal form of a more prevalent disease of variable intensity. It was pointed out that the mild form of the disease might be detected only by careful examinations of the blood and occasionally by alterations in the roentgenograms.

The evidence in this and in other reported families [2] indicated that the disease was transmitted directly from parent to child. In the previous study, it was suggested that the children of a parent with the mild form of the disease ran the risk of inheriting the disease in any of its clinical forms. It was pointed out that the hereditary aspects, which were so clearcut in this case, were not unique and had been found in many other families. It is the purpose of this paper to add corroborative evidence on the hereditary relationships of the disease and to emphasize the method by which the milder forms are detected. The alterations in the blood will be described in parents and children of 15 additional families with Mediterranean anemia. The importance of a careful study of the blood picture cannot be overestimated, since it usually represents the sole means by which the mild form of disease may be identified. The implications of the occurrence of cases of mild Mediterranean anemia are obvious in communities with large Italian and Greek populations.

From the New York Hospital, and the Department of Pediatrics, Cornell University Medical College.

1. Smith, C. H.: Mediterranean (Cooley's) Anemia in a Youth of Nineteen Years Observed Since Early Childhood, J. Pediat. **20**:370 (March) 1942.

2. (*a*) Caminopetros, J.: Recherches sur l'anémie érythroblastique infantile des peuples de la Méditerranée orientale; étude anthropologique, étiologique et pathogénique; la transmission héréditaire de la maladie, Ann. de méd. **43**:104 (Feb.) 1938. (*b*) Atkinson, D. W.: Erythroblastic Anemia: Report of Two Cases in Adult Siblings, with Review of Theories as to Its Transmission, Am. J. M. Sc. **198**:376 (Sept.) 1939. (*c*) Wintrobe, M. M.; Matthews, E.; Pollack, R., and Dobyns, B. M.: A Familial Hematopoietic Disorder in Italian Adolescents and Adults Resembling Mediterranean Disease (Thalassemia), J. A. M. A. **114**:1530 (April 20) 1940. (*d*) Strauss, M. B.; Daland, G. A., and Fox, H. J.: Familial Microcytic Anemia: Observations on Six Cases of Blood Disorder in an Italian Family, Am. J. M. Sc. **201**:30 (Jan.) 1941.

It will be shown that the hematologic changes in the mildest forms probably represent a trait analogous to traits already established for sickle cell anemia and to a more limited degree for congenital hemolytic jaundice. The family histories included in this study confirm the suggestion offered in the earlier study that the trait of Mediterranean anemia is transmitted as a dominant characteristic.

TABLE 1.—*Studies of the Blood in the Family of J. A.*

	Mother (M. A.)	Patient (J. A.)	Brother (D. A.)
Age, years	42	2	18
Hemoglobin, Gm./100 cc. of blood	11.8	7	13
Red blood cells, millions/cu. mm.	4.0	3.70	5.6
Volume of packed red blood cells, cc./100 cc. of blood	42	21	46
Mean red cell volume, cubic microns	105	57	82
Hemoglobin concentration in red cells, per cent	28	33	28
Icteric index	..	14	..
Stippling, average number of cells/100 oil immersion fields	4.5	4	3
Reticulocytes, per cent	2	2.5	0.5
Target cells	0	+	+
Anisocytosis, poikilocytosis	+	+++	+
Nucleated red blood cells/100 white blood cells	0	12	0
Fragility test:			
Hemolysis began	0.4	0.4	0.4
Hemolysis ended	0.25	0.25	0.25

Comment.—J. A., a 2 year old boy, was noted to have an enlarged spleen and anemia at 5½ months. The anemia became more severe; the spleen continued to enlarge, and frequent transfusions were required. The features were typically mongoloid. Sternal aspiration revealed a hyperplastic marrow with a count of 244,000 nucleated cells per cubic millimeter, of which 84 per cent were normoblasts. The patient died at 3 years of age. A brother died at 11 months with severe anemia. The healthy brother, D. A., 19½ years of age, and the parents were born in Sicily.

TABLE 2.—*Studies of the Blood in the Family of C. A.*

	Mother (C. A.)	Patient (C. A.)
Age, years	28	1
Hemoglobin, Gm./100 cc. of blood	13	6
Red blood cells, millions/cu. mm.	5.49	3.04
Volume of packed red blood cells, cc./100 cc. of blood	40	26
Mean red cell volume, cubic microns	79	86
Hemoglobin concentration in red cells, per cent	33	23
Icteric index	..	..
Stippling, average number of cells/100 oil immersion fields	6.5	75
Reticulocytes, per cent	..	..
Target cells	0	++
Anisocytosis, poikilocytosis	++	+++
Nucleated red blood cells/100 white blood cells	0	148
Fragility test:		
Hemolysis began	0.375	0.45
Hemolysis ended	0.25	0.2

Comment.—C. A., a girl 2 years of age, was observed to have an enlarged spleen and anemia at 5 months. Frequent transfusions were required. The facies was typically mongoloid. The spleen was removed at 14 months of age. This child died of pneumonia at 33 months of age. The mother was American born of Italian parentage. The husband and his parents were born in Italy. The parents were first cousins.

RESULTS

The data have been compiled in tables which summarize the important hematologic features for each family. The headings refer to the first member of the family to seek medical care because of anemia. Investigation of the entire family usually revealed that this member suffered from a more severe form of anemia than any of his siblings or parents.

To conserve space, only a single typical examination of the blood chosen from a larger series has been included for each subject. The summaries appended to each table include only the pertinent data concerning the history of the affected children and of the parents and grandparents.

TABLE 3.—*Studies of the Blood in the Family of A. B.*

	Father (N. B.)	Mother (C. B.)	Patient (A. B.)	Sister (B. B.)
Age, years	58	42	3	6
Hemoglobin, Gm./100 cc. of blood	11.8	12.5	9.2	10.5
Red blood cells, millions/cu. mm.	5.94	4.70	4.16	5.33
Volume of packed red blood cells, cc./100 cc. of blood	44	37	33	35
Mean red cell volume, cubic microns	74	79	79	66
Hemoglobin concentration in red cells, per cent	27	34	28	30
Icteric index	..	..	5.1	9.4
Stippling, average number of cells/100 oil immersion fields	2	0	4	3
Reticulocytes, per cent	1	0.5	2.0	3.0
Target cells	+	0	+	+
Anisocytosis, poikilocytosis	++	0	++	++
Nucleated red blood cells/100 white blood cells	0	0	0	0
Fragility test:				
Hemolysis began	0.375	0.425	0.375	0.375
Hemolysis ended	0.225	0.3	0.225	0.225

Comment.—A. B., a boy 3 years of age, one of seven children, was observed to have an enlarged spleen and anemia at 2½ months. The spleen did not become larger, and at times it could not be palpated. Sternal aspiration at 2½ months showed a total count of 95,000 nucleated cells per cubic millimeter, of which 40 per cent were normoblasts. Antianemia therapy over prolonged periods was without value. Both parents were natives of Sicily. The sister, B. B., 4 years of age, had a normal facies, and the spleen was not palpable.

TABLE 4.—*Studies of the Blood in the Family of A. C.*

	Mother (G. C.)	Patient (A. C.)
Age, years	26	1½
Hemoglobin, Gm./100 cc. of blood	11.6	10.8
Red blood cells, millions/cu. mm.	5.22	5.19
Volume of packed red blood cells, cc./100 cc. of blood	39	39
Mean red cell volume, cubic microns	75	75
Hemoglobin concentration in red cells, per cent	30	28
Icteric index	..	6
Stippling, average number of cells/100 oil immersion fields	3	3.5
Reticulocytes, per cent	1.5	4.5
Target cells	0	0
Anisocytosis, poikilocytosis	+	++
Nucleated red blood cells/100 white blood cells	0	0
Fragility test:		
Hemolysis began	0.45	0.425
Hemolysis ended	0.275	0.25

Comment.—In the case of A. C., a 2 year old boy, pallor was noted at 1 year. The spleen was not felt. The mother was American born of Italian parentage. The father and his parents were born in Italy.

TABLE 5.—*Studies of the Blood in the Family of I. C.*

	Father (C. C.)	Mother (C. C.)	Patient (I. C.)	Brother (C. C.)	Sister (A. C.)
Age, years	48	48	7	7	16
Hemoglobin, Gm./100 cc. blood	14	12	6.5	12.5	12
Red blood cells, millions/cu. mm.	5.6	6.15	2.7	6.1	4.5
Volume of packed red blood cells, cc./100 cc. of blood	43	36	22	40	42
Mean red cell volume, cubic microns	77	59	81	66	93
Hemoglobin concentration in red cells, per cent	33	33	30	31	29
Icteric index	17.4	6	30	10	13.6
Stippling, average number of cells/100 oil immersion fields	65	3.5	16	13	0
Reticulocytes, per cent	4.5	..	8	0.5	2
Target cells	0	0	+++	0	0
Anisocytosis, poikilocytosis	+	++	+++	+	0
Nucleated red blood cells/100 white blood cells	0	0	196	0	0
Fragility test:					
Hemolysis began	0.4	0.4	0.4	0.4	0.425
Hemolysis ended	0.25	0.25	0.15	0.25	0.325

Comment.—I. C., a 7½ year old girl, was observed to be pallid and to have a greatly enlarged spleen at 1 year. In addition, the patient had a transposition of the heart, liver and spleen. The child's facies became typically mongoloid. Transfusions were given from an early period and had to be repeated at frequent intervals. Since splenectomy was performed at 4 years of age, transfusions were less frequent. Prior to operation sternal aspiration showed 93 per cent normoblasts. After splenectomy this was reduced to 66 per cent. The peripheral blood showed, however, a greatly increased number of normoblasts and enormous red cells which were exceedingly thin (fig. 3). The parents were both Sicilians and were first cousins. The blood of the twin brother showed moderate hematologic changes (fig. 4), but his spleen was barely palpable, his appearance was normal and he appeared healthy.

TABLE 6.—*Studies of the Blood in the Family of F. DeP.*

	Father (J. DeP.)	Mother (A. DeP.)	Patient (F. DeP.)	Brother (J. J. DeP.)	Sister (R. DeP.)
Age, years	38	36	3½	5	10
Hemoglobin, Gm./100 cc. blood	13.5	12	7	9.2	11
Red blood cells, millions/cu. mm.	4.72	5.59	6.07	5.19	5.21
Volume of packed red blood cells, cc./100 cc. of blood	40	37	29	33	40
Mean red cell volume, cubic microns	85	66	48	64	77
Hemoglobin concentration in red cells, per cent	34	32	24	28	28
Icteric index	..	14	7.5	9	10
Stippling, average number of cells/100 oil immersion fields	0	4	3	7	28
Reticulocytes, per cent	0.5	4.5	1.5	2.5	6
Target cells	0	+	++	+	0
Anisocytosis, poikilocytosis	0	++	++	++	++
Nucleated red blood cells/100 white blood cells	0	0	0	0	0
Fragility test:					
Hemolysis began	0.425	0.4	0.375	0.35	0.45
Hemolysis ended	0.325	0.25	0.2	0.25	0.25

Comment.—F. DeP., a girl 4½ years of age, showed pallor at 2 years. The spleen was never palpable. Prolonged antianemia therapy was without value in elevating the hemoglobin concentration. In the brother J. DeP., 6 years of age, the spleen was occasionally palpable. The sister, R. DeP., 10 years of age, appeared healthy, and splenomegaly was not noted. The parents were American born, but all the grandparents were natives of Sicily.

TABLE 7.—*Studies of the Blood in the Family of A. DiB.*

	Father (J. DiB.)	Mother (T. DiB.)	Patient (A. DiB.)	Brother (P. DiB.)
Age, years	30	29	6	3½
Hemoglobin, Gm./100 cc. of blood	13	11	6	10.5
Red blood cells, millions/cu. mm.	5.98	5.02	2.37	5.78
Volume of packed red blood cells, cc./100 cc. of blood	40	38	23	38
Mean red cell volume, cubic microns	67	76	97	66
Hemoglobin concentration in red cells, per cent	33	29	26	28
Icteric index	6	7.8	30	11.5
Stippling, average number of cells/100 oil immersion fields	4	1	9	3
Reticulocytes, per cent	2.5	1.5	4	2.5
Target cells	0	0	+	+
Anisocytosis, poikilocytosis	+	+	+++	+
Nucleated red blood cells/100 white blood cells	0	0	9	0
Fragility test:				
Hemolysis began	0.4	0.375	0.4	0.35
Hemolysis ended	0.25	0.25	0.2	0.25

Comment.—A. DiB., a 6 year old boy, had anemia, and an enlarged liver and spleen were noted at 3 years and 8 months. The spleen became progressively enlarged; the facies became typically mongoloid, and frequent transfusions were necessary. P. DiB., the brother, 4 years of age, appeared healthy, and splenomegaly was not noted. The parents are American born, while all the grandparents were natives of Sicily.

TABLE 8.—*Studies of the Blood in the Family of J. F.*

	Mother (J. F.)	Patient (J. F.)	Brother (M. F.)	Sister (M. F.)
Age, years	34	4	7	9
Hemoglobin, Gm./100 cc. of blood	11	5	10	13
Red blood cells, millions/cu. mm.	5.29	2.31	5.45	4.50
Volume of packed red blood cells, cc./100 cc. of blood	41	20	35	41
Mean red cell volume, cubic microns	78	87	64	91
Hemoglobin concentration in red cells, per cent	27	25	29	32
Icteric index	8	30	15	..
Stippling, average number of cells/100 oil immersion fields	5	12	6	0
Reticulocytes, per cent	2.5	6	4	0.5
Target cells	+	++	0	0
Anisocytosis, poikilocytosis	+	+++	++	0
Nucleated red blood cells/100 white blood cells	0	269	0	0
Fragility test:				
Hemolysis began	0.4	0.4	0.4	0.425
Hemolysis ended	0.275	0.15	0.25	0.325

Comment.—J. F., a boy aged 4½ years, exhibited anemia and an enlarged spleen at 4½ months. The anemia became progressive, and intensive transfusion was required. The facies were mongoloid. The splenomegaly became more pronounced. Splenectomy was performed at 13 months of age. Prior to operation sternal aspiration revealed 81 per cent of normoblasts. One month after splenectomy this value dropped to 28 per cent but rose to 67 per cent subsequently. The peripheral blood after the operation showed large numbers of normoblasts and thin red cells of greatly increased size. The brother, M. F. 7½ years of age, appeared healthy, and his spleen could not be palpated. Both parents were born in Sicily.

All the children in this study were born in the United States with the exception of D. A. (table 1), who was born in Sicily. Fourteen families were of Italian and two of Greek origin, but not every parent in whom the mild form of anemia

TABLE 9.—*Studies of the Blood in the Family of M. G.*

	Father (C. G.)	Mother (F. G.)	Patient (M. G.)
Age, years	35	27	1
Hemoglobin, Gm./100 cc. of blood	15	10	10
Red blood cells, millions/cu. mm.	5.89	5.47	6.15
Volume of packed red blood cells, cc./100 cc. of blood	48	32	33
Mean red cell volume, cubic microns	81	59	54
Hemoglobin concentration in red cells, per cent	31	31	30
Icteric index	10	3	10
Stippling, average number of cells/100 oil immersion fields	0	6	5
Reticulocytes, per cent	1	2.5	3
Target cells	0	+	0
Anisocytosis, poikilocytosis	0	++	++
Nucleated red blood cells/100 white blood cells	0	0	0
Fragility test:			
Hemolysis began	0.45	0.35	0.35
Hemolysis ended	0.325	0.25	0.2

Comment.—M. G., a boy 2 years of age, was noted to be pallid at 15 months. The spleen was never palpable. The facies was not mongoloid. Intensive antianemia therapy was without effect on the hemoglobin concentration. Both parents were American born, but all grandparents were born in Italy.

TABLE 10.—*Studies of the Blood in the Family of D. M.*

	Father (P. M.)	Mother (D. M.)	Patient (D. M.)	Brother (S. M.)	Patient (S. M.)
Age, years	53	44	18¾	16½	7¾
Hemoglobin, Gm./100 cc. blood	12	13	8	11.8	9
Red blood cells, millions/cu. mm.	4.31	5.26	3.75	6.13	3.36
Volume of packed red blood cells, cc./100 cc. of blood	43	44	34	43	30
Mean red cell volume, cubic microns	99	83	90	70	89
Hemoglobin concentration in red cells, per cent	28	30	24	27	30
Icteric index	15	4	23	..	6
Stippling, average number of cells/100 oil immersion fields	2	2	2	3	2
Reticulocytes, per cent	2	4	4.5	2.5	7
Target cells	+	0	+	0	+
Anisocytosis, poikilocytosis	+	+	+++	+	+++
Nucleated red blood cells/100 white blood cells	0	0	8	0	8
Fragility test:					
Hemolysis began	0.4	0.425	0.4	0.375	0.425
Hemolysis ended	0.25	0.325	0.25	0.25	0.225

Comment.—This family was reported on in detail in another communication.[1] For completeness of the present study its outstanding features will be mentioned.

The 3 children were American born, and the parents were natives of Sicily. D. M., male, was 20 years of age at the latest observation. At 4 years he was observed to be extremely listless and to have no appetite. Examination revealed Cooley's anemia of an advanced grade. He was severely anemic; the spleen and liver were enlarged, and a loud systolic murmur was heard over the entire precordium. The facies was mongoloid. Transfusions were required until he was 7 years of age. Since that time the patient had been clinically well, although physical examination still revealed a greatly enlarged spleen, moderate anemia and characteristic roentgenographic changes. The brother S. M., 9 years of age at the latest examination, showed evidences of anemia at 6 months and an enlarged spleen at 2 years and 9 months. His appearance became mongoloid. Although he had never had a transfusion, he showed the clinical, roentgenographic and hematologic features of a classic case of Cooley's anemia of moderate severity. Antianemia therapy over prolonged periods was without value. The remaining brother, S. M., 17½ years of age, had always been in excellent health and appeared normal. His spleen was not enlarged. In addition to hematologic changes, roentgen examination showed skeletal alterations in the right elbow similar to those of his affected brothers. This was most noticeable in the ulna and consisted of a trabeculated zone of osteoporosis 5 cm. from the proximal end of this bone.

was detected was born in either of these countries. Nine of the affected parents were born in the United States, but in every instance all grandparents of this group were natives of Sicily or Greece. In one family the disease was detected in three generations (fig. 2, table 14). All parents were healthy, and nothing in their

appearance suggested the mongolian facies of their affected children. In none of the parents who were examined was the spleen palpable. In the mother of A. C. (table 4) and the parents of S. S. (table 16) an enlarged spleen had been noted at some previous period.

TABLE 11.—*Studies of the Blood in the Family of A. and N. P.*

	Father (C. P.)	Mother (P. P.)	Patient (A. P.)	Patient (N. P.)
Age, years	48	28	1½	1½
Hemoglobin, Gm./100 cc. of blood	12	12	7.5	6.5
Red blood cells, millions/cu. mm.	..	5.9	3.0	3.48
Volume of packed red blood cells, cc./100 cc. of blood	50	46	22	20
Mean red cell volume, cubic microns	..	78	73	57
Hemoglobin concentration in red cells, per cent	24	26	34	33
Icteric index	..	..	37	40
Stippling, average number of cells/100 oil immersion fields	5.5	1.5	4.5	9
Reticulocytes, per cent	..	..	4	2
Target cells	0	0	++	++
Anisocytosis, poikilocytosis	++	+	+++	+++
Nucleated red blood cells/100 white blood cells	0	0	22	18
Fragility test:				
Hemolysis began	0.4	0.4	0.325	0.325
Hemolysis ended	0.275	0.25	0.1	0.1

Comment.—These male twins were born in the United States, and their parents were born in Greece. A. P., 2 years of age, was observed to be anemic at 4 months. At 18 months splenomegaly was pronounced, and the blood and roentgenographic changes were those of a severe type of Cooley's anemia. Transfusions were required frequently. Sternal aspiration showed a total count of 147,200 nucleated cells per cubic millimeter, of which 83 per cent were normoblasts. In the twin, N. P., pallor was noted at 3 months and splenomegaly at 11 months. At 18 months he showed an advanced grade of Cooley's anemia, as did his brother, and frequent transfusions were also necessary. The sternal aspiration showed 138,800 nucleated cells per cubic millimeter, of which 75 per cent were normoblasts. Both twins showed typical mongoloid features.

TABLE 12.—*Studies of the Blood in the Family of J. P.*

	Father (J. P.)	Mother (C. P.)	Patient (J. P.)	Patient (R. P.)	Sister (P. P.)
Age, years	34	29	3½	5	6½
Hemoglobin, Gm./100 cc. blood	12	11	8.5	7.5	11.5
Red blood cells, millions/cu. mm.	5.51	5.39	3.8	3.2	5.45
Volume of packed red blood cells, cc./100 cc. of blood	41	38	29	25	38
Mean red cell volume, cubic microns	74	71	76	78	70
Hemoglobin concentration in red cells, per cent	29	29	29	30	30
Icteric index	7.5	6.8	14	37	6.8
Stippling, average number of cells/100 oil immersion fields	20	7	7	10	5
Reticulocytes, per cent	5	3	6	..	4
Target cells	+	+	+	++	++
Anisocytosis, poikilocytosis	+	++	++	+++	+
Nucleated red blood cells/100 white blood cells	0	0	0	12	0
Fragility test:					
Hemolysis began	0.425	0.4	0.4	0.4	0.375
Hemolysis ended	0.25	0.25	0.2	0.225	0.25

Comment.—J. P., a 4 year old boy, was observed to have an enlarged spleen when he was 6 weeks old, and anemia was noted at 6 months. The anemia and splenomegaly became more pronounced, and frequent transfusions were required. Sternal aspiration showed a hyperplastic marrow with 74 per cent normoblasts. R. P., a sister 5½ years of age, was noted to be pallid at 5 months. The spleen showed a progressive increase in size. Anemia became more severe, and frequent transfusions were required. Sternal aspiration showed a hyperplastic marrow with 83 per cent normoblasts. P. P., another sister, 7 years of age, showed a slight anemia. The edge of the spleen was palpable at the costal margin. No transfusions were required. J. P. and R. P. had typical mongoloid features, whereas in P. P. they slightly suggested mongolism. The father was American born of Sicilian parents. The mother was born in Sicily.

It was not possible in every instance to examine all the members of a family but examinations of the blood were made for 63 individuals in sixteen families, including the family previously reported on (table 10). Analysis of the tables and the genetic summary included in figure 1 confirms the familial transmission of

Mediterranean anemia previously described in the family of D. M. (table 10). In every one of the sixteen families definite changes were found in the blood of at least one parent and in one or more of their children. Among the siblings the

TABLE 13.—*Studies of the Blood in the Family of F. R.*

	Father (F. R.)	Mother (M. R.)	Patient (F. R.)	Patient (M. R.)	Sister (J. R.)	Sister (V. R.)
Age, years	37	31	4	6	11	¾
Hemoglobin, Gm./100 cc. blood	14	12	8.5	9.8	13.5	9.8
Red blood cells, millions/cu, mm.	5.9	5.5	3.1	4.2	4.18	5.58
Volume of packed red blood cells, cc./100 cc. of blood	42	40	32	34	43	34
Mean red cell volume, cubic microns	71	73	103	81	103	61
Hemoglobin concentration in red cells, per cent	33	30	27	29	31	29
Icteric index	9.3	6	21	7.5	10	30
Stippling, average number of cells/100 oil immersion fields	0	17.5	2	4	0	5
Reticulocytes, per cent	4	1	0.5	1.5	..	1.7
Target cells	0	0	+	+	0	+
Anisocytosis, poikilocytosis	0	++	++	++	0	++
Nucleated red blood cells/100 white blood cells	0	0	0	0	0	0
Fragility test:						
Hemolysis began	0.4	0.4	0.375	0.375	0.425	0.35
Hemolysis ended	0.325	0.25	0.25	0.275	0.3	0.225

Comment.—In F. R., a boy 4½ years of age, anemia and palpable spleen were noted at 8 months. The spleen became moderately enlarged. Sternal aspiration at 16 months revealed a count of 140,000 nucleated cells per cubic millimeter, with 38 per cent normoblasts. A sister, M. R., 7 years of age, had a palpable spleen at 1½ years. Anemia was first noted at 3 years. Prolonged antianemia therapy was ineffective with both patients. Their features suggested a mongoloid appearance. V. R., a sister 11 months of age, was observed at 9 months to have a palpable spleen and a moderate anemia. The mother was American born of Sicilian parents. The father was born in Sicily.

TABLE 14.—*Studies of the Blood in the Family of A. and J. S.*

	Father (J. S.)	Mother (M. S.)	Patient (A. S.)	Patient (J. S.)	Father's Father (J. S.)	Father's Mother (A. S.)	Mother's Father (A. M.)	Mother's Mother (B. M.)
Age, years	27	30	2½	2½	64	58	60	52
Hemoglobin, Gm./100 cc. blood	15.5	11	9	8	13.5	12	11	10
Red blood cells, millions/cu. mm.	4.62	5.03	5.33	..	4.55	4.86	4.39	4.72
Volume of packed red blood cells, cc./100 cc. of blood	48	38	34	34	40	39	38	38
Mean red cell volume, cubic microns	104	76	64	..	88	80	87	81
Hemoglobin concentration in red cells, per cent	32	29	26	24	34	31	29	26
Icteric index	4.7	10	15	5	7.3	7.2	6	7
Stippling, average number of cells/100 oil immersion fields	0	2	5.5	2	0	0	2	0
Reticulocytes, per cent	3	3.5	2	1.5	0.75	0.5	1	0.25
Target cells	0	0	+	0	0	0	+	0
Anisocytosis, poikilocytosis	0	+	++	+++	0	0	+	+
Nucleated red blood cells/100 white blood cells	0	0	0	0	0	0	*	0
Fragility test:								
Hemolysis began	0.45	0.4	0.4	0.425	0.4	0.4	0.4	0.425
Hemolysis ended	0.325	0.275	0.25	0.25	0.3	0.3	0.275	0.325

*One nucleated red cell was observed in the smear.

Comment.—J. S. and A. S. are male twins 3½ years of age. J. S. was admitted to the hospital at 2½ years because of a foreign body in a bronchus. At that time routine examination revealed a palpable spleen and anemia. Sternal aspiration showed a hyperplastic marrow with 234,000 nucleated cells per cubic millimeter, of which 42 per cent were normoblasts. Examination of the twin brother, A. S., revealed comparable clinical, hematologic and roentgenographic changes. The parents and grandparents were born in Sicily. It will be observed in the tables that hematologic changes were noted in the mother and in her father.

extent of hematologic, clinical and roentgenographic alteration varied in degree from the mild and asymptomatic form to that displayed by the severely anemic patient requiring periodic transfusions. Some of the affected siblings, like the

parents, were entirely without symptoms, while others attracted attention because of pallor and a palpable spleen.

The blood of both parents was studied in twelve families, and in nine of these all the siblings were examined. It will be observed that in nine families at least one sibling had the classic form of Mediterranean anemia. In six of the remaining families at least one sibling came under observation because of a refrac-

TABLE 15.—*Studies of the Blood in the Family of D. S.*

	Father (F. S.)	Mother (M. S.)	Patient (D. S.)	Brother (J. S.)
Age, years	51	43	7½	17
Hemoglobin, Gm./100 cc. of blood	14.5	12	10	11
Red blood cells, millions/cu. mm.	4.5	5.2	5.7	4.74
Volume of packed red blood cells, cc./100 cc. of blood	45	36	32	40
Mean red cell volume, cubic microns	100	69	56	84
Hemoglobin concentration in red cells, per cent	32	33	31	28
Icteric index	10	5	5	10
Stippling, average number of cells/100 oil immersion fields	0	28	8	20
Reticulocytes, per cent	1	3.5	4.5	3.5
Target cells	0	0	+	+
Anisocytosis, poikilocytosis	0	++	++	++
Nucleated red blood cells/100 white blood cells	0	0	0	0
Fragility test:				
Hemolysis began	0.45	0.425	0.4	0.375
Hemolysis ended	0.35	0.25	0.225	0.25

Comment.—D. S., a boy, was 8¾ years of age. At 5 years of age anemia had been noted which could not be corrected with intensive therapy. At 8 years, sternal aspiration had revealed a hyperplastic marrow, showing 257,000 nucleated cells per cubic millimeter, with 45 per cent normoblasts. He possessed a mongoloid appearance. The brother, J. S., 18 years of age, appeared healthy, and splenomegaly had not been noted. The parents were born in Sicily.

TABLE 16.—*Studies of the Blood in the Family of S. S.*

	Father (J. S.)	Mother (S. S.)	Patient (S. S.)
Age, years	47	36	3
Hemoglobin, Gm./100 cc. of blood	12	11	8
Red blood cells, millions/cu. mm.	4.08	5.8	2.576
Volume of packed red blood cells, cc./100 cc. of blood	46	34	25
Mean red cell volume, cubic microns	113	59	97
Hemoglobin concentration in red cells, per cent	26	32	32
Icteric index	6.5	6.8	18
Stippling, average number of cells/100 oil immersion fields	11	10	3
Reticulocytes, per cent	3	6	2
Target cells	+	0	++
Anisocytosis, poikilocytosis	++	++	++
Nucleated red blood cells/100 white blood cells	0	0	22
Fragility test:			
Hemolysis began	0.4	0.4	0.375
Hemolysis ended	0.225	0.225	0.175

Comment.—S. S. is a girl 4 years of age. Anemia was first noted when she was 6 months old. At latest examination this patient had extreme splenomegaly, and the blood and roentgenographic changes were those of a severe type of Cooley's anemia. Periodic transfusions had been necessary. A brother died at 1½ years of severe anemia. The parents were born in Greece.

tory anemia. In the family of A. and J. S. (table 14), the anemia was discovered in the first twin, J. S., in the course of treatment for another condition. Subsequent study revealed its presence in the other twin, in the mother and in the maternal grandfather (fig. 2).

In figure 1, the data concerning members of the sixteen families have been arranged graphically to represent the severity of the disease. It will be noted in this chart that the blood of 54 of the 63 persons was abnormal; 12 were severely anemic, and 42 had the mild type of the disease. The hematologic changes in the

affected parent or sibling consisted of varying degrees of hypochromic anemia, occasionally polycythemia, an elevated icteric index, the presence of target cells and stippled red cells, abnormal numbers of reticulocytes and macrocytes, and increased resistance of erythrocytes to hypotonic solutions of sodium chloride.

As noted in figure 1, in every family with a severely affected child both parents showed abnormalities of the blood. This happened in six families; but, while this

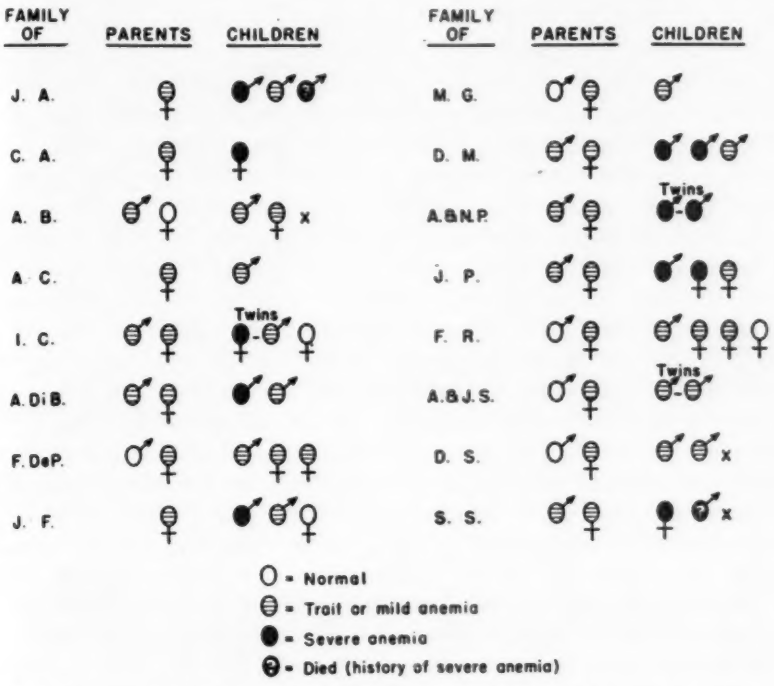

Fig. 1.—The inheritance of Mediterranean (Cooley's) anemia in the sixteen affected families.

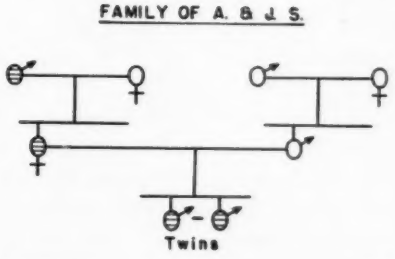

Fig. 2.—Transmission of Mediterranean anemia in three generations of family of A. and J. S. (table 14).

correlation is suggestive, it cannot be regarded as a universal rule, since an exception had already been observed in incomplete studies of one unreported family. It will be noted that the families of J. A. and of S. S. included one member who had died previously of a severe anemia. According to the parents, the clinical manifestations in these children were similar to those of their living siblings.

A slight to moderate reduction in hemoglobin content with a normal or slightly decreased volume of packed red cells characterized the blood of the majority of persons with the mild type of Mediterranean anemia, the affected parent and the

sibling alike. The lower hemoglobin content relative to the hematocrit reading is expressed in the tables by the hemoglobin concentration of the red cells, which represents the percentage ratio of hemoglobin in grams to the volume of packed red cells in 100 cc. of blood. Hemoglobin concentrations under the minimal normal value of 32 per cent and ranging between 24 and 31 per cent will be noted in the tables for the majority of persons possessing the mild form of this disease. In the children with the moderate or severe form of anemia the hemoglobin content and the volume of packed red cells were both considerably reduced, which usually caused a low mean hemoglobin concentration.

The measurement of the volume of packed red cells by the hematocrit constitutes an important index in comparative studies of all anemias. This determination, which reflects the total mass of cells in a unit volume of blood, is of special significance in Mediterranean anemia, in which considerable alterations occur in the size, shape and thickness of the red cells. A volume of packed red cells of 36 cc. per hundred cubic centimeters of blood may be regarded as the minimum normal level for the younger children in this study, with values ranging to approximately 42 cc. for adults. For the children who were moderately or severely anemic, low hematocrit measurements were invariably obtained. In the group of those with the mild form of the disease, normal levels were found for all of the older children, while for the younger children the values were either normal or slightly decreased. With few exceptions (F. G., 32 per cent, table 9; S. S., 34 per cent, table 16; C. C., 36 per cent, table 5, and M. S., 36 per cent, table 15) the larger number of affected adults showed a normal volume of packed red cells.

The great variation in the mean volume of red cells, which serves as an index of size of the cells, is apparent in the tables. Allowing for differences which are dependent on the age of the subject, available studies indicate that a cell volume of 80 cubic microns represents the minimal size for the majority of the subjects included in this study. On this basis, subnormal values were found for 17 of 21 affected parents and for 15 of 19 children with the mild form of the disease. Since the mean volume of red cells represents the ratio between the volume of packed red cells and the erythrocyte count, the smaller size of cell in the mild form usually resulted from an increased number of red cells as compared with a normal or slightly lowered volume of packed red cells. While the mean size of the cells connotes a tendency to microcytosis in patients with the mild form, a distinguishing feature of all smears was the interspersion of red cells of large size. Hypochromic and polychromatophilic macrocytes, occasionally target-cell-like in appearance, constituted an important diagnostic feature and were found in varying numbers in all smears, even in those predominantly microcytic.

Of the 12 children with severe anemia, the mean red cell volume fell below normal in 5 and was normal or greater than normal in the remainder. In the smears of all of these patients large numbers of excessively thin achromic macrocytes of unusual proportions were noted.

Stippled red cells were observed in all blood smears regardless of the degree of anemia. On each slide at least 250 oil immersion fields were examined. Even when the disease was mild these cells were sometimes so profuse as to approximate levels found in lead poisoning, but this condition could be readily eliminated. In 6 persons in the group (C. C., table 5; R. DeP., table 6; J. P., table 12; M. R., table 13, and M. S. and J. S., table 15) stippled red cells were found in numbers ranging from 17 to 65 per hundred microscopic fields. Target cells (figs. 3 and 6) were by no means a constant accompaniment in the 54 persons with abnormal blood pictures. They were noted in the smears of 33 and were absent in those of 21.

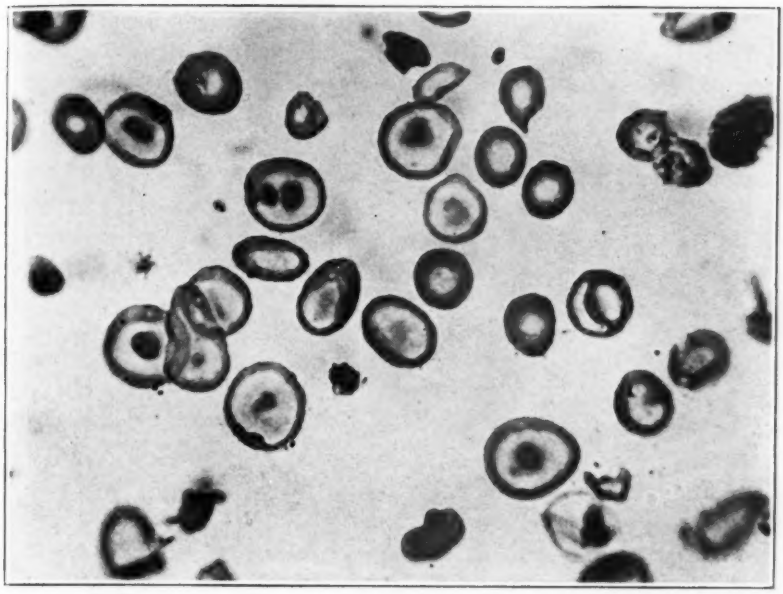

Fig. 3.—Photomicrograph of a blood smear of I. C., the severely anemic twin (table 5). Note excessive size of cells, marked hypochromia, target corpuscles, a normoblast and abnormal thinness as indicated by transparency, wrinkling and ridges (× 900).

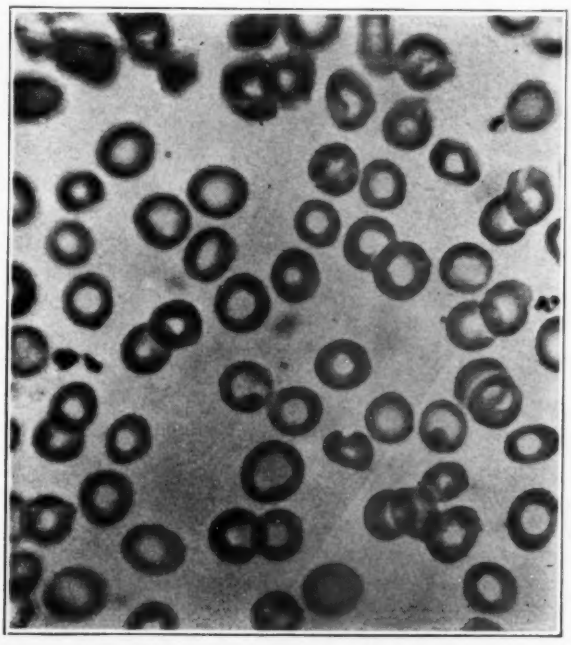

Fig. 4.—Photomicrograph of a blood smear of C. C., twin of I. C. (figure 1), with the mild form of the disease. Note poikilocytosis, anisocytosis, hypochromia and a macrocyte in the lower part of the field. Other hematologic features are noted in table 5 (×800).

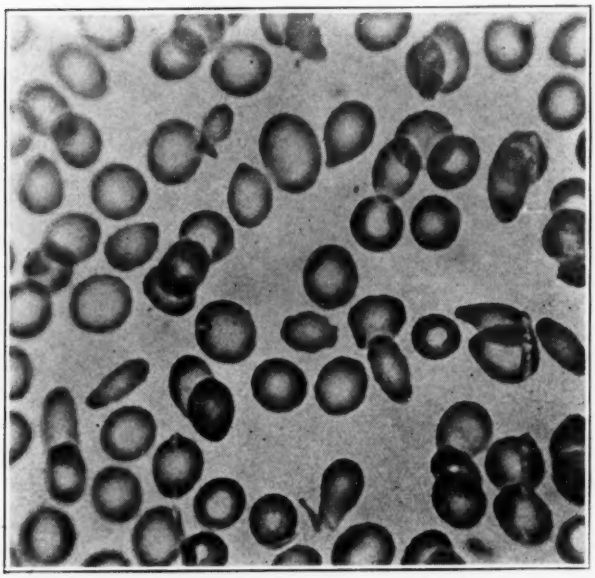

Fig. 5.—Photomicrograph of a blood smear of C. P. (table 12), a parent with the trait of Mediterranean anemia. Note poikilocytosis, anisocytosis, hypochromia and flattened and oval cells. The macrocytes of the form observed in the upper part of the field were present in varying numbers in smears of all patients, even in those predominantly microcytic (× 900).

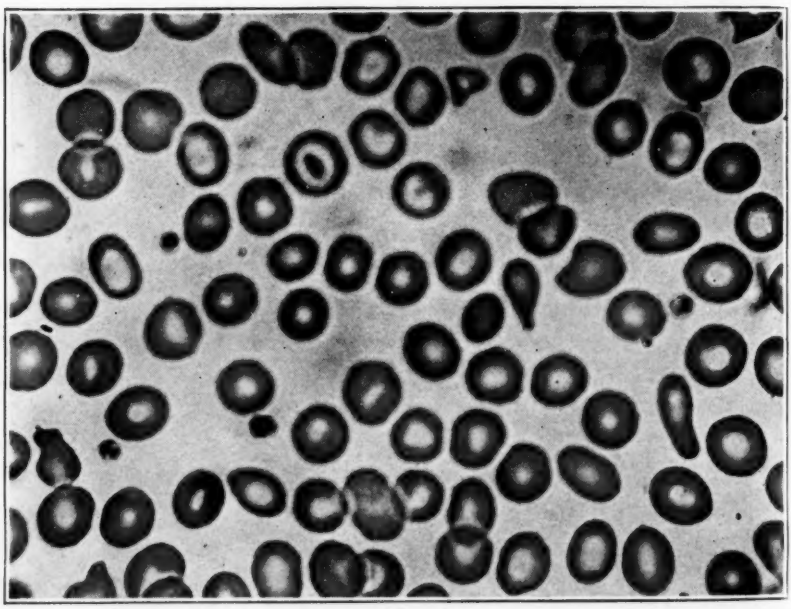

Fig. 6.—Photomicrograph of a blood smear of M. S. (table 15), a parent with the trait of Mediterranean anemia. Note anisocytosis, poikilocytosis, a flattened cell in the lower part of the field and a target corpuscle in the upper part. The blood of this patient showed 28 stippled red cells per 100 microscopic fields (× 900).

Red cell counts of 6,000,000 per cubic millimeter and above were noted for 5 subjects with the mild form of the disease (mother C. C. and brother C. C., table 5; F. DeP., table 6; M. G., table 9, and brother S. M., table 10). Erythrocytosis was not, however, a constant feature noted in every examination of blood of the same person. Forty-five of the affected persons for whom the icteric index was determined had values above 6 in 34 of the examinations made, with the highest values in the most severely anemic patients.

An increase in reticulocytes occurred in all patients with anemia, and the highest counts were equally distributed among those with the mild and those with the severe type of the disease. Of 39 reticulocyte counts of patients with the mild type, 27 showed levels of 2 per cent or above, while 12 fell within the normal range. In severely anemic patients the reticulocytes varied from 2 to 8 per cent, but in some instances the numbers of these cells were probably increased above the recorded levels, since their recognition was often difficult because of the poor staining qualities of the deformed cells.

Nucleated red cells were noted in the smears of all the children who were severely anemic. While they were not observed in the count for J. P. recorded in table 12, they were present in other smears from this patient. It will also be observed that a normoblast was noted in the smear of A. M. (table 14), the grandfather with the mild anemia. They were not noted in the smears of other persons with the mild form of the disease.

The fragility test probably constitutes the most important single laboratory procedure in the diagnosis of Mediterranean anemia, particularly of the milder type. For that reason, a careful comparison with a control and a microscopic examination of the unhemolyzed cells in the tubes with the more dilute saline solutions are recommended. With the exception of mother D. M. (table 10), all other subjects with the mild or the severe form of the disease showed a prolongation of the span of fragility of the red cells. It was noted that in the suspected case the tubes containing 0.35 and 0.325 per cent of sodium chloride showed a much heavier sediment of intact red cells and a supernatant fluid that was less hemolyzed than the corresponding tubes of the control. Even with macroscopic end points at 0.25 per cent of sodium chloride, unhemolyzed cells were frequently found microscopically in the tubes from subjects with the mild form in 0.175 per cent solution and in tubes from subjects with the severe form in lower concentrations. In the control test, hemolysis usually began in 0.425 per cent solution of sodium chloride and was complete in the tube with the 0.325 per cent solution.

COMMENT

The more complete data provided by the present study confirmed the observations made with the single family previously reported on,[1] as well as those of a number of recent contributions.[3] Furthermore, the discovery of Mediterranean anemia in 54 persons in sixteen families made available sufficient information to permit classification of the disease according to types. In addition, this investigation served to perfect the method by which the milder forms of the disease may be detected and also to emphasize its hereditary aspects.

The procedure followed in this study was to examine clinically, hematologically and roentgenographically the siblings and parents of all children suspected of having

3. Pierce, M. I.: Erythroblastic Anemia: A Clinical Study, Am. J. Dis. Child. **61**:654 (March) 1941. Footnote 2.

or having overt Mediterranean anemia. In each family, therefore, there was at least one child who either had the classic type of the disease or had a milder but refractory type of anemia. It soon became apparent that the disease originally described by Cooley was the severe and readily recognizable form of a more widespread disease. The mild type occurred in healthy persons and escaped clinical notice, but its importance as a potential source for hereditary transmission of the disease in any of its forms cannot be overestimated. While the moderately or severely anemic patients revealed clearcut clinical abnormalities, the children and parents with the mild form of the disease were usually asymptomatic and the condition was identified solely by examination of the blood. The persons with the mild form were healthy and possessed a normal appearance; their spleens were not enlarged. In this group belonged the affected parents and usually the siblings who were examined because of the discovery of a well defined form of Mediterranean anemia in a brother or sister. Another group who were also regarded as having a mild disease included children who attracted attention because of pallor and who revealed lowered hemoglobin and hematocrit readings and occasionally a palpable spleen.

Since the recognition of the mild type usually depended on a careful survey of the blood, an analysis of the more important hematologic data for persons with this type will be reviewed. The most common findings, regardless of the severity of the anemia, were anisocytosis and poikilocytosis, stippling and increased resistance to hypotonic solution of sodium chloride. Hypochromic and polychromatophilic macrocytes (figs. 4 and 5) constituted an important diagnostic feature and were frequently found in predominantly microcytic blood smears. Flattened or oval red cells of normal size were commonly observed in the smears of patients with the mild form of the disease (figs. 5 and 6). The occurrence of morphologic changes far in excess of the extent of the anemia, as noted by Wintrobe,[2c] constitutes a fundamental principle in the detection of the mild form, and this observation was amply corroborated in the present study.

Stippled red cells were observed in all patients with the mild form, sometimes in excessive numbers. For example, in one of the parents (father C. C., table 5) the blood showed 14 Gm. of hemoglobin per hundred cubic centimeters and 43 per cent by volume of packed red cells, both within the normal range, yet the stippled cells averaged 65 per hundred microscopic fields. This observation is difficult to reconcile with the concept of stippling as an index of regeneration, since there appears to be little need for accelerated formation of blood in the absence of anemia. Furthermore, examination of the tables reveals that excessive stippling did not always occur in numerical relation to reticulocytosis, which is also a sign of increased hemopoiesis. For these reasons, the intervention of another factor, such as a structural abnormality of the red cell, may be postulated. Stippling in this disease may therefore reflect, not an immaturity of the red cell, but a corpuscular defect which is either degenerative or congenital in nature.

In recent years there has been a tendency to overestimate the diagnostic importance of the target cell in Mediterranean anemia. This relationship originated with a report by Dameshek[4] of an Italian youth with the mild form of this disease, which he designated as "target cell" anemia because the smear contained numerous target cells. This cell had been observed earlier by Haden and Evans[5] in sickle

4. Dameshek, W.: "Target Cell" Anemia: Anerythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445 (Oct.) 1940.

5. Haden, R. L., and Evans, F. D.: Sickle Cell Anemia in White Race: Improvement in Two Cases Following Splenectomy, Arch. Int. Med. **60**:133 (July) 1937.

cell anemia and was first described by Barrett [6] as a target cell because of its deeply stained center and periphery arranged in concentric light and dark zones. He noted that target corpuscles possessed increased resistance to hypotonic solutions of sodium chloride and that this characteristic was related to their thinness, since they possessed a relatively large cell envelope as compared with their volume. These cells were first identified in the smears of Cooley's anemia by Bywaters [7] and by Smith,[8] without any claim that they were specific cells in this disease. Target cells may be found in increased numbers in sickle cell anemia, obstructive jaundice and hypochromic anemia, in many anemic states in infants and children and sometimes following splenectomy.[9] Bohrod [10] recently pointed out that the target cell is a hyperresistant young cell and occurs as a nonspecific response to destruction of blood. He showed that it was more likely to be present in larger numbers in the more chronic anemias and that it could not be regarded as representing the fundamental defect in Cooley's anemia. Cooley, in the discussion of his presidential address before the American Pediatric Society,[11] has also recently said that target cells do not bear a specific relation to Mediterranean anemia and observed that decreased fragility of the red cells does not depend on their presence. This conclusion was confirmed, moreover, in the present investigation, since target cells occurred in but one half of the patients with the mild form despite an increased resistance to hypotonic solutions in all but 1 of them. Furthermore, microscopic examination of the sediment in the tubes containing the extremely dilute solutions of sodium chloride in the fragility test frequently failed to reveal bowl-shaped cells, the forerunners of the target cells. The weight of evidence points, therefore, to the target corpuscle as a nonspecific cell, and what was designated as "target cell" anemia should more appropriately be classified among the mild types of Mediterranean anemia.

The fragility test represents the most useful single method for detecting the person with the mild type of Mediterranean anemia. The original observations of Caminopetros [2a] in bringing to light entire families with this disease through the medium of the fragility test have been amply supported in this and other investigations. As stated in the previous report, thinness of the red cell may represent the fundamental structural defect of the erythrocytes in Mediterranean anemia. The increased resistance to hemolysis in hypotonic solutions of sodium chloride, where the erythrocytes are subjected to critical osmotic changes, supports the concept of thinness of the red cells. The persistence of intact cells in the residue of tubes beyond the macroscopic end point further attests to their abnormal thinness.

This quality of thinness is most conspicuous in the macrocytic cells (fig. 3) which characterize the blood in advanced stages of Mediterranean anemia, particu-

6. Barrett, A. M.: Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, J. Path. & Bact. **46**:603 (May) 1938.

7. Bywaters, E. G. L.: The Cooley Syndrome in an English Child, Arch. Dis. Childhood **13**:173 (June) 1938.

8. Smith, C. H.: Anemias of Early Infancy: Pathogenesis and Diagnosis, J. Pediat. **16**:375 (March) 1940.

9. Singer, K.; Miller, E. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man, Am. J. M. Sc. **202**:171 (Aug.) 1941. Miller, E. B.; Singer, K., and Dameshek, W.: Experimental Production of Target Cells by Splenectomy and Interference with Splenic Circulation, Proc. Soc. Exper. Biol. & Med. **49**:42 (Jan.) 1942.

10. Bohrod, M. G.: The Significance of Target Cells in Anemia, Am. J. M. Sc. **202**:869 (Dec.) 1941.

11. Cooley, T. B.: (*a*) Hereditary Factors in the Blood Dyscrasias: President's Address, Am. J. Dis. Child. **62**:1 (July) 1941; (*b*) discussion, p. 8.

larly after splenectomy.[12] Their cytologic appearance has been described elsewhere,[8] but it may be briefly reviewed because of their frequent occurrence in the microcytic smears of patients with a mild form of the disease. Occasionally macrocytes possess a target appearance (fig. 3), and it is only under these circumstances that they are more suggestive of Mediterranean anemia. The target corpuscle may represent one form of thin cell. A second type of macrocyte (fig. 3) is round or occasionally somewhat oval with a narrow rim of hemoglobin and a large central achromic area. The third, and most specific, type is the pale leaflike erythrocyte staining poorly and often reaching an unusual size. The hemoglobin is sparse and irregularly distributed in small islands, but its thinness is expressed in the ridges and in wrinkling of the corpuscle. In wet preparations the edges of the cell may be observed to fold over, and the several layers possess a remarkable transparency (fig. 3). With the exception of a few direct measurements,[12] thinness of the cells in Mediterranean anemia has, however, been inferred from the response to the fragility test and by examination of wet and stained smears. If future studies confirm this morphologic quality of the cell by actual measurement in larger numbers of cases, Mediterranean anemia may justifiably be designated as "thin cell or leptocytic anemia."

The fact that Mediterranean anemia of all grades of severity proved refractory to treatment often aided in its diagnosis, particularly in the mild form. In some of the cases of the less severe form, those of A. B. (table 3); F. DeP. (table 6); M. G. (table 9); F. R. and M. R. (table 13) and D. S. (table 15) in which the disease was at first regarded as nutritional anemia, it was later suspected of being Mediterranean anemia when it was observed that antianemia agents were ineffective in elevating the hemoglobin or hematocrit values or in otherwise altering the blood picture. The failure of treatment of these children led to an investigation of other members of the family with the discovery of the familial incidence of the anemia. Large doses of iron were administered to 2 of the affected parents (mother C. C., table 5, and mother F. G., table 9) for long periods with a complete lack of response. As a general rule it was found that when an infant or young child of Italian or Greek parentage who was free from infection failed to respond to adequate iron therapy, the subsequent course was usually consistent with that of Mediterranean anemia. Similarly for an adult, it is obvious that the diagnosis of this disease should be considered for persons of Mediterranean origin with a mild or moderate anemia which has resisted treatment and which had heretofore been unclassified. While anemias of diverse cause can occur in these persons, the probability of Mediterranean anemia will be further increased by the discovery of other afflicted persons in the same family.

Sternal aspirations which were performed on persons with the mild or the severe form of the disease were indicative of hyperplasia of the bone marrow. In each instance the smear revealed a normoblastic picture, usually a pronounced elevation in the count of nucleated cells, and the same erythrocytic abnormalities as in the peripheral blood were noted.

Roentgenographic studies were made in conjunction with the hematologic examinations. Routine studies were usually limited to examination of the skull and hands, with the exception of the family of D. M. (table 10), in which the

12. Bradford, W. L., and Dye, J.: Observations on the Morphology of the Erythrocyte in Mediterranean Disease: Thalassemia (Erythroblastic Anemia of Cooley), J. Pediat. 9:279 (Sept.) 1936.

bones about the elbows were also included. Usually the degree of skeletal change was correlated with the severity of the anemia. Thus, in children with the mild form of the disease minimal involvement of bone was noted, whereas in the severely anemic subjects with well developed signs early in life the skeletal changes were more extensive. The later in childhood the disease became manifest, the less pronounced was the osteoporosis. When the course was prolonged in the severe forms, an increase in trabecular bone appeared within the areas of osteoporosis. While this process was readily discernible in grossly altered bones, in the milder forms osteosclerosis also tended to obliterate the evidences of minimal degrees of decalcification. It is obvious that in older children and in adults with mild forms of Mediterranean anemia no roentgenographic changes would be expected. In affected parents, even with severe abnormalities of the blood, the changes in the bones were usually absent or equivocal. In a few instances lateral roentgenograms of the skull of such a person showed a slightly enlarged diploic space, which appeared finely granular or mottled. It is noteworthy that in D. M.'s healthy brother, S. M. (table 10), with the mild form of the disease a trabeculated zone of osteoporosis was observed at the proximal portion of the ulna similar to that present in his severely anemic brothers. In patients with established anemia and in some with the milder form the bony changes produced by hyperplasia of the marrow were reflected in the metacarpal bones by varying degrees of widening of the medullary canals with cortical thickening, giving them an appearance of fulness and of rectangular contour.

It should be pointed out that although the sixteen families in this study were of Italian or Greek origin not every affected parent was born in one of these two countries. In eight of the families one or both of the affected parents were born in the United States, but in every instance all grandparents were natives of Sicily. While the existence of the trait in three generations was determined in only one family in the present study, further investigations would probably reveal a more extensive familial transmission. The birth of a parent in Italy or Greece need no longer be regarded, however, as a requisite for the diagnosis of Mediterranean anemia in the child.

In the previous communication [1] healthy persons possessing the hematologic abnormalities of the mild form were designated as carriers of the disease, since they constituted the source of inheritance. This term was not employed in the strict genetic sense but was used to describe the asymptomatic subject with the mild type of anemia that ordinarily escaped detection. It was pointed out that a person with minimal hematologic and roentgenographic alterations is "fully equivalent, genetically speaking, to his sick sibling so that the children of both run the same risk of inheriting Mediterranean anemia in any of its clinical forms." Analysis of the case histories in the present study, especially those in which the course had been followed for a period of years, has added confirmation to the validity of this concept. As a parallel with other blood dyscrasias it is apparent that the hematologic features of the mild form may be said to represent a trait similar to traits already established for sickle cell anemia and to a more limited degree for congenital hemolytic jaundice. The existence of mild forms of the disease without symptoms corresponds to similar states in both of these diseases.

The determination of the incidence of the trait of Mediterranean anemia awaits large scale investigation, but such studies will be attended with greater technical difficulties than are involved in investigation of other blood dyscrasias. Contrary

to sickle cell anemia and congenital hemolytic jaundice, in which characteristic cells are found, there is no single cell that may be regarded as specific for Mediterranean anemia. The evidence for the existence of the trait depends on the identification of a number of abnormalities in the blood smear and of prolonged fragility spans, often with little or no reduction of hemoglobin. As already stated, future studies may reveal that thin, flat cells represent the basic morphologic feature of Mediterranean anemia, corresponding to sickle cells, elliptic cells and spherocytes. Until sufficient data are collected, this peculiarity of the red cells must be sought in the blood smear and in the fragility test.

While the number and size of the families in this sample are small, the family histories included in this study are not inconsistent with previous suggestions that the trait of Mediterranean anemia is transmitted as a dominant characteristic. At first glance the high incidence of this condition noted in this series compels caution in interpreting the results from a strictly hereditary point of view. On the other hand, an environmental factor, such as occurs in pellagra or goiter, is difficult to prove, since all but 1 of the children and 9 of the affected parents were born in the United States. Local toxic factors may also be excluded on that basis, and a history of malaria was not obtained for any affected parent. Cooley [11] suggested the possibility of the instability of certain genes and increased susceptibility to mutations in areas where diseases of the spleen, liver and bone marrow are frequent.

Since this material was selected because of the detection of at least 1 affected child and since in no instance were both parents free from the disease, it would indicate that recessive inheritance could be excluded. It is recognized, however, that the number of families in this series is relatively small, and a larger sample might show cases in which both parents were unaffected. The case for a recessive mechanism can be made even stronger, because of the sixteen families two were the result of marriage of first cousins, a frequency considerably above that for the general population. On the other hand, as Roberts [13] has suggested, consanguineous marriages might prove coincidental among families inhabiting isolated areas where such marriages are common. This would be particularly applicable to Cooley's anemia, in which with few exceptions the persons primarily affected originated in Sicily and Greece. Added support for the dominant form of inheritance also comes from the recent studies of McIntosh and Wood.[14] In a comprehensive genetic analysis of a large number of carefully chosen families, they have shown that the mechanism of heredity could be explained by the association of two dominant genes. Whereas the anemia syndrome results from the simultaneous operation of both genes in one person, the increased resistance of erythrocytes to hemolysis in the affected parent may reflect the expression of only one of these.

In the course of this investigation certain clinical phases of Mediterranean anemia were encountered which may be briefly considered at this point. As with other chronic anemias, murmurs and moderate enlargement of the heart were frequently observed in children with Mediterranean anemia, which suggested primary heart disease. The additional complaints of pains in the bones and joints in severely anemic children and at times in persons with a more moderate anemia suggested rheumatic heart disease. The causation of the latter symptoms may be

13. Roberts, J. A. F.: An Introduction to Medical Genetics, New York, Oxford University Press, 1940, p. 83.

14. McIntosh, R., and Wood, C. L.: An Inquiry into the Genetic Factor in Cooley's Anemia, Am. J. Dis. Child. **64**:192 (July) 1942.

explained on the basis of encroachment on the inelastic bony skeleton by expanding and hyperplastic marrow, somewhat similar to the mechanism described in childhood leukemia.[15] In Mediterranean anemia as in sickle cell anemia,[16] in which the same difficulties of differential diagnosis occur, the cardiac changes are more likely to depend on the persistent profound anemia rather than on rheumatic heart disease.

The prognosis of Mediterranean anemia is contingent on the fact that the disease shows a continuous range of variation from the mildest form, represented by the trait, to the advanced form, marked by severe anemia. It is the child whose anemia is severe and in whom splenomegaly and skeletal changes are progressive early in life for whom the chances of survival beyond puberty are poorest. Even for this type of child the prognosis must be guarded, for in the patient previously reported on,[1] now 20 years of age, the anemia became arrested in childhood at blood levels compatible with well-being. For the larger group of patients with the mild form of the disease, prolonged survival may now be predicted, particularly with the knowledge that the parents may be similarly affected. The person who has no symptoms goes through life normally and without medical attention.

One of the major problems associated with the management of the established form of Mediterranean anemia is that of maintaining blood levels which are compatible with normal activity. While it is obvious that optimum hemoglobin and hematocrit levels are desirable to sustain maximum cardiovascular efficiency, this goal is difficult to attain in the advanced type of Mediterranean anemia. In the absence of a specific remedial agent, periodic transfusion still remains the sole therapeutic measure in the severe condition. The need for blood replacement may become so acute that multiple transfusions at short intervals are required. Following the administration of blood a gradual drop occurs to a lower level, which remains relatively constant for a varying period, after which there is a further decline necessitating treatment. In the chronic condition of lesser severity, subnormal levels are reached which without treatment have proved adequate for the performance of normal activities. In the course of this study, hemoglobin and hematocrit estimations were carried out periodically for several years for patients with the chronic form of the disease. It is hoped that an analysis of these data, to be reported in a subsequent communication, will serve to define a hematologic range within which the patient with the severe form of Mediterranean anemia may live comfortably without transfusions.

SUMMARY

In sixteen families with Mediterranean anemia, 63 persons were examined and 54 revealed abnormalities of the blood. Twelve, all children, were severely anemic, and 42, including parents and siblings, had the mild type of this condition. In every one of the sixteen families definite changes in the blood occurred in at least one parent, and in one family changes were noted in three generations.

While all available siblings and parents of patients with Mediterranean anemia were examined clinically, hematologically and roentgenographically, the recognition

15. Smith, C. H.: Leucemia in Childhood with Onset Simulating Rheumatic Disease, J. Pediat. **7**:390 (Sept.) 1935.

16. King, J. T., Jr., and Janeway, C. A.: Sickle Cell Anemia with Cardiac Complications, Internat. Clin. **3**:41 (Sept.) 1937. Klinefelter, H. F.: The Heart in Sickle Cell Anemia, Am. J. M. Sc. **203**:34 (Jan.) 1942.

of the mild type depended solely on a careful study of the blood. These changes consisted of varying degrees of hypochromic anemia, occasionally polycythemia, an elevated icteric index, the presence of target cells, reticulocytes, macrocytes and stippled red cells, and increased resistance of the red cells to hemolysis. The most common findings, regardless of the severity of the anemia, were anisocytosis and poikilocytosis, basophilic stippling and increased resistance to hypotonic sodium chloride solution. Hypochromic and polychromatophilic macrocytes constituted an important diagnostic feature and were frequently found in predominantly microcytic blood smears.

Target cells were by no means a constant accompaniment in all cases, and it was shown that they appeared in only half of the patients with mild forms of the disease. Target corpuscles are nonspecific cells, and there appears to be no justification for designating any anemia by their presence. Thinness and flatness of the cells, on the other hand, may represent the fundamental structural defect of the erythrocytes in Mediterranean anemia. This quality was inferred from their resistance to hemolysis in hypotonic solutions of sodium chloride and by direct examination of wet and stained smears.

Persons with the mild form of the disease were without symptoms and appeared in perfect health and the condition would have escaped detection without careful scrutiny of the blood. The occurrence of morphologic changes of the red cells far in excess of the extent of anemia constitutes a fundamental principle in the detection of this type.

The degree of skeletal change was usually correlated with the severity of the anemia. In affected parents, the changes in the bones were usually absent or equivocal. In children with mild forms of the disease minimal involvement of the bones was noted. The earlier the onset, the more severe was the anemia and the more extensive were the skeletal changes. The later in childhood the disease became manifest, the less severe was the osteoporosis. In the milder forms osteosclerosis tends to obliterate the evidences of minimal degrees of decalcification. It is obvious, therefore, that in older children and in adults with mild forms of Mediterranean anemia, no significant roentgenographic changes can be expected.

In every family with a severely anemic child, both parents showed abnormalities of the blood. This happened in six families, but it was pointed out that this cannot be regarded as a universal rule.

The data suggest that certain features of the blood in Mediterranean anemia may be said to represent a trait similar to traits already established for sickle cell anemia and to a more limited degree for congenital hemolytic jaundice. The evidence for the existence of the trait in Mediterranean anemia depends on the identification of a number of abnormalities in the blood smear and of a prolonged fragility span, since there is no single cell that may as yet be regarded as specific for Mediterranean anemia. The fact that Mediterranean anemia of all grades of severity proves refractory to treatment often aids in its diagnosis, particularly of the milder form, and this is further corroborated by the discovery of the familial incidence of the anemia.

The children of a parent with the trait run the risk of inheriting the disease in any of its clinical forms, from the mildest to the most severe. Since the disease appears to be transmitted directly from parent to child, the implications of the existence of mild forms of Mediterranean anemia are obvious in communities with large Italian and Greek populations.

While the number and size of the families in this sample are small, the pedigrees included in this study suggest that the trait of Mediterranean anemia is transmitted as a dominant characteristic.

The prognosis of Mediterranean anemia depends on the fact that the disease manifests a continuous range of variation, from the mildest form, represented by the trait, to the advanced types marked by severe anemia. The evidence supports the view that the advanced and well recognized form of Cooley's anemia represents a severe and often fatal form of a more widespread disease of variable intensity.

SULFADIAZINE

REVIEW OF ITS USE IN TREATMENT OF CHILDREN

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Late in the summer of 1941 sulfadiazine was supplied to the Milwaukee Children's Hospital for clinical investigation of its use in treatment of and its effect on infants and children.[1] At that time there were only a few articles available in the literature on this new sulfonamide compound and most of them related to its use experimentally in animals. There were several articles which reviewed its use for human patients, and most of these reports dealt glowingly with the absence of toxic effects and the relative nontoxicity of this new drug.[2] However, there was little to draw from as to its efficacy against the usual infections seen in a children's hospital or as to the dosage to employ for consistently satisfactory blood levels. With this in mind, the present study was undertaken, and the results and conclusions were presented in an abbreviated form before the Milwaukee County Medical Society at its meeting April 10, 1942.

CHEMISTRY

Sulfadiazine is related to its direct ancestors, sulfapyridine and sulfanilamide. Its chemical name is 2-(paraaminobenzenesulfonamido)-pyrimidine. In sulfapyridine one of the hydrogens of sulfanilamide is replaced by a pyridine. In sulfadiazine one of the hydrogens of sulfanilamide is replaced by a pyrimidine.

On Feb. 28, 1942 the Council on Pharmacy and Chemistry of the American Medical Association announced its acceptance of sulfadiazine for inclusion in New and Nonofficial Remedies.[3]

LABORATORY STUDIES

The sulfadiazine supplied was used only on "house" patients cared for directly by the resident and attending staff of the Milwaukee Children's Hospital. Only 2 patients are included from the private services because of the inability to perform routine laboratory examinations necessary for this study without added expense to the patient. We attempted to perform the following laboratory work and observation on each patient receiving sulfadiazine:

1. Performance of a complete blood count and urinalysis on alternate days or more often if indications arose.

From Milwaukee Children's Hospital and Marquette University School of Medicine.

1. The sulfadiazine and the sulfadiazine in triethanolamine used in this study were supplied by the Lederle Laboratories, Inc.

2. Plummer, N., and Ensworth, H. K.: Absorption and Excretion of Sulfadiazine, Proc. Soc. Exper. Biol. & Med. **45**:734 (Nov.) 1940. Peterson, O. L.; Strauss, E.; Taylor, F. H. L., and Finland, M.: Absorption, Excretion and Distribution of Sulfadiazine, Am. J. M. Sc. **201**:357 (March) 1941. Finland, M.; Strauss, E., and Peterson, O. L.: Sulfadiazine, J. A. M. A. **116**:2641 (June 14) 1941.

3. Sulfadiazine, report of the Council on Pharmacy and Chemistry, J. A. M. A. **118**: 730 (Feb. 28) 1942.

2. Determination of the level of free sulfadiazine in the blood (expressed as milligrams per hundred cubic centimeters) every second or third day or as indicated with change of dosage.

3. Making of cultures for the offending organism, for most of which material was taken from one or more of the following sources: throat, blood, spinal fluid, ear, pleural fluid and open wounds.

4. Observation for toxic symptoms other than those revealed in the laboratory, such as cutaneous rashes, mental disturbances, vomiting, etc. These are probably the hardest to determine in children. Both subjective and objective observations are difficult to evaluate because of the large amount of vomiting by sick infants and children, the difference in mental reactions to hospitalization by children and the multitude of evanescent rashes seen on infants and children.

TABLE 1.—*Diseases and Diagnoses for Which Sulfadiazine Was Used*

	Cases		Cases
Osteomyelitis	11	Epidemic encephalitis	1
Chronic	4	Poliomyelitis	1
Acute	7	Fracture of skull	2
Pneumonia	13	Basal	1
Bronchopneumonia	6	Compound depressed	1
Lobar pneumonia	7	Abscess of brain	1
Multiple pulmonary abscess	1	Cellulitis of face	6
Bronchitis and laryngotracheobronchitis	9	Perinephric abscess	1
Pharyngitis	16	Pyelitis	3
Tonsillitis	7	Septicemia	2
Acute otitis media	11	Dacryocystitis	1
Postpneumonic pleural effusion	3	Ruptured appendix with generalized peritonitis	1
Empyema	3	Impetigo	2
Cervical adenitis	5		
Peritonsillitis	1	Complicating Diseases Present Before Treatment	
Axillary adenitis	1	Hemophilia	1
Meningitis	8	Pertussis	1
Tuberculous	1	Gastroenteritis	4
Streptococcic	1	Paronychia	1
Serous	1	Rheumatic heart disease	1
Influenzal	2	Nephritis	1
Meningococcic	1	Cystic hydroma	1
Pneumococcic	1	Pulmonary tuberculosis	1
Lymphocytic choriomeningitis	1		

MATERIAL FOR STUDY

The hospital records of 115 patients were reviewed for this study. Because of the incompleteness of laboratory data on some of the charts, the final study and conclusions are drawn from a review of 90 patients treated between September 1941 and April 1942.

No attempt was made to select subjects or to observe control groups for comparison. The patients receiving sulfadiazine were the average sick pediatric hospital patients. The only unintentional selection of subjects receiving sulfadiazine could be accounted for as follows:

1. Practically all patients who were severely and critically ill received sulfadiazine on entrance.

2. Patients who were already receiving another sulfonamide compound and not responding to treatment were given sulfadiazine.

The great variety of diseases and infections which were treated with sulfadiazine and also concomitant diseases which were present are shown in table 1. Fortunately for us, during this study a number of patients with meningitis entered the hospital, and we were able to judge the effect of sulfadiazine in the spinal fluid on this small series.

The patients varied in age from 3 weeks to 13 years and in weight from 6½ to 86 pounds (2.9 to 39 Kg.).

RESULTS OF CULTURES AND RESPONSE TO SULFADIAZINE

For many of the patients we were unable to identify any specific offending organism; most of them had cultures of material from the throat showing mixed flora or had pneumonia with untyped pneumococci. We had no previous controlled series of subjects treated with other sulfonamide compounds with which to compare the response of various bacteria and diseases with those obtained in the present study, nor did we study a control series of patients while using sulfadiazine. Therefore, we can comment only from our clinical observations as to the efficacy of sulfadiazine and the response to its administration.

The following specific organisms were obtained by culture from the patients who were treated with sulfadiazine

. . . . . .

1. Infections of Throat

   Culture of material from the throat—pure hemolytic streptococci—2 patients.
   Patients responded as well as to other sulfonamide compounds.

2. Empyema

   (*a*) Culture of pleural fluid—hemolytic streptococci—1 patient.

   (*b*) Culture of pleural fluid—untyped pneumococci—2 patients.

   All presented typical pictures of empyema, eventually had rib sections and open drainages and made fairly rapid and complete recoveries.

3. Septicemia alone

   (*a*) {Culture of blood—meningococci / Culture of spinal fluid—no organisms} 1 patient.

   Patient had unexplained meningococcemia, found during diagnostic work-up, and responded rapidly to sulfadiazine.

   (*b*) {Culture of blood—Haemophilus influenzae / Culture of material from the throat—pure H. influenzae} 1 patient.

   Patient entered the hospital with an acute obstructive laryngitis. He presented the exact picture described by Sinclair [4] in his report on a series of cases with similar cultures. Our patient responded quickly enough, through the use of sulfadiazine administered by mouth and by rectum plus steam and oxygen, to avert the necessity of a tracheotomy, which seemed imminent on entrance.

4. Chronic recurrent pyelitis

   Culture of urine—Escherichia coli—1 patient.

   Previously this chronic condition had always cleared immediately with hospitalization and use of a sulfonamide compound, and it cleared promptly again with sulfadiazine.

5. Perirenal abscess

   Culture of pus—Staph. aureus haemolyticus—1 patient.

   The patient had surgical drainage of the abscess and recovered nicely with oral administration of sulfadiazine and supportive treatment.

6. Abscess of the hard palate

   Culture of pus—Staph. aureus haemolyticus—1 patient.

   This could almost be classified as a localized osteomyelitis. With surgical drainage and sulfadiazine the patient recovered without further extension.

4. Sinclair, S. E.: Haemophilus Influenzae Type B in Acute Laryngitis with Bacteremia, J. A. M. A. **117**:170 (July 19) 1941.

7. Osteomyelitis

(*a*) Chronic
Cultures of blood—Staph. aureus haemolyticus—1 patient.

(*b*) Acute, with surgical intervention.
Culture of blood—Staph. aureus haemolyticus—1 patient.

(*c*) Acute, without surgical intervention.
Culture of blood—Staph. aureus haemolyticus—3 patients.
From this group of patients some of our most interesting results were obtained. As a whole, sulfadiazine seemed to be effective against the hemolytic Staph. aureus. Following the report by Hoyt, Davis and Van Buren [5] on the treatment of acute osteomyelitis by the use of sulfonamide compounds without surgical intervention, we took the same risk with our patients by using sulfadiazine as the effective drug and blood transfusions as the most useful adjunct. We had no fatalities among our patients with osteomyelitis. We were fortunate in seeing and treating 1 child with disputed and 3 with undisputed acute osteomyelitis; all recovered without surgical operation on the bone and with the use of the previously mentioned procedures and symptomatic measures. Following are brief reports of the 3 cases of undisputed acute osteomyelitis.

CASE 1.—The patient was a 22 month old girl and weighed 24 pounds (10.9 Kg.). Roentgen examination disclosed osteomyelitis of a femur. Culture of the blood yielded Staph. aureus haemolyticus. He received 12 Gm. of sulfadiazine in six days and then remained afebrile. Skin traction was continued for three weeks, after which he was discharged home as recovered.

CASE 2.—The patient was a 12 year old boy who weighed 51 pounds (23.1 Kg.). Culture of the blood revealed Staph. aureus haemolyticus. Roentgenograms revealed osteomyelitis of a femur after two weeks. The patient was given sulfadiazine orally on entrance to the hospital. After his temperature became normal, he was given small maintenance doses of sulfadiazine probably longer than necessary; but, because of our inexperience with this form of treatment, we wanted to be sure that all infection had subsided. He received a total of 208 Gm. of sulfadiazine over a period of eighty-one days. It required nearly ten days to bring the acute symptoms under control. Traction seemed to give the greatest relief from pain and spasm. The patient was discharged after five months of hospitalization, walking and clinically well and with no surgical scar, disabling cast or draining sinus. Roentgen changes were still present, and the blood sedimentation rate remained rapid.

CASE 3.—This girl was 10 years old and weighed 65 pounds (29.5 Kg.). Culture of her blood revealed Staph. aureus haemolyticus. The patient was given sulfadiazine orally after a two day trial of sulfathiazole. After about a week a roentgenogram showed early osteomyelitis of the spinous process of the third lumbar vertebra. Her temperature became normal in nine days. After ten days a small, localized, superficial abscess developed under the skin over the third lumbar vertebra. This was incised and drained, and culture of the pus showed Staph. aureus haemolyticus. This patient was kept on a small maintenance dose of sulfadiazine for over two months, when a roentgenogram showed some healing of the bony process. She was then clinically well and asymptomatic.

8. Meningitides

(*a*) Tuberculous—result of guinea pig inoculation, positive—1 patient.
This patient did not respond to sulfadiazine and died.

(*b*) Pneumococcic—1 patient.
Culture of the spinal fluid—Pneumococcus type III.
Culture of material from the throat—Pneumococcus type III.

5. Hoyt, W. A.; Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcus Osteomyelitis, J. A. M. A. **117**:2043 (Dec. 13) 1941.

Culture of blood—negative result (second day).

This 3½ year old patient entered the hospital in a moribund condition after having signs of meningitis at home for nearly one week. She responded well to sulfadiazine originally but went into coma and convulsions and died after two weeks. Culture of her spinal fluid never became negative. Necropsy revealed a thick, plastic exudate over the entire base and side of the brain.

(*c*) Streptococcic—1 patient.

Culture of spinal fluid—hemolytic streptococci.

Culture of blood—negative result.

This 3½ year old patient entered the hospital in an apparently moribund condition. He was given sulfathiazole orally for nearly twenty-four hours with no change in condition. He was then changed to sulfadiazine orally in heavy doses, and in twenty-four hours he was sitting up in bed, eating and alert. In another twenty-four hours culture of the spinal fluid yielded no organisms.

(*d*) Meningococcic—1 patient.

Spinal fluid—unable to subculture before recovery.

This 3 year old patient also entered in an apparently moribund condition with a temperature of 106 F. The spinal fluid showed over 10,000 white blood cells with only a few gram-negative diplococci. He was given heavy doses of sulfadiazine orally, over 2 grains per pound (0.27 Gm. per kilogram) per twenty-four hours, and then took fluids very poorly. Unfortunately, the spinal fluid became clear of organisms so rapidly that by the next spinal tap we were unable to obtain a positive culture. This patient had our only critical reaction to the drug. In three days his urine was half packed with red blood cells and crystals. After two more days he began to have oliguria, vomiting, slight pain and tenderness in the flanks and an elevated blood pressure. His nonprotein nitrogen level was 101 mg. and his creatinine level 7.4 mg. per hundred cubic centimeters. The use of sulfadiazine was discontinued immediately. Cystoscopy was performed and revealed some crystals clinging to the mucosa of the bladder. The right ureter was open and easily catheterized and lavaged; the left ureteral opening could not be seen or found for catheterization because severe edema and inflammation were present in this region. Fluids and alkali were forced orally, and fluids were given intravenously. In two days the patient was in no distress, was urinating freely and had a nonprotein nitrogen level of 56 and a creatinine level of 0.6 mg. per hundred cubic centimeters. He was discharged as recovered.

(*e*) Influenzal—2 patients.

Cultures of spinal fluid—H. influenza, type B.

Cultures of blood—H. influenzae, type B.

The recovery of these 2 patients with the use of sulfadiazine and anti-H. influenzae serum has already been described in another paper.[6]

DOSAGE OF SULFADIAZINE

When sulfadiazine was first received for clinical use we had little to guide us in attempting to establish dosage for children. The *Bulletin of Lederle Laboratories* recommended blood levels of 7 to 10 mg. per hundred cubic centimeters for adults, based on previous experimental and clinical work. We had to rely completely on the scale of dosage according to age prepared by Hodes and cited in that bulletin.[7] The dosage routine of Hodes was as follows:

"Infants under 6 months of age—0.5 Gm. initial dose and 0.25 Gm. every 6 hours. Infants 6 months to 3 years—1.0 Gm. initial dose and 0.5 Gm. every 6 hours. Children 3 to 10 years—2.0 Gm. initial dose and 1.0 Gm. every 6 hours."

6. Greenthal, R. M., and Winters, K. J.: Influenzal Meningitis: Report of Two Cases, Arch. Pediat. **60**:69 (Feb.) 1943.

7. Hodes, H.: Clinical Use of Sulfadiazine, Bull. Lederle Lab. **9**:40 (July) 1941.

We started our doses according to this routine, but because of the great difference in size, weight and fluid intake of the children we varied the dose or the interval between doses according to (1) the blood levels obtained, (2) the results of blood counts and urinalyses and (3) the severity of the disease.

Because of these difficulties, this paper was originally prompted by an attempt to correlate the weight of patients with their oral dosage and with their blood levels. The results of this correlation will be found in table 2.

Our maximum oral doses to date have been:

1. For acute osteomyelitis without surgical intervention, 208 Gm. over eighty-one days.

2. For acute osteomyelitis without surgical intervention, 108 Gm. over seventy-eight days.

3. For chronic osteomyelitis with surgical intervention, 105.5 Gm. over fifty-five days.

TABLE 2.—*Relation of Concentration of Sulfadiazine in Blood and Size of Oral Dose*

24 Hr. Dosage, Grains per Pound	Total Number of Levels	Range of Blood Levels, Mg./100 Cc.	Concentration of Blood Levels, Mg./100 Cc.*	Modal Blood Level,† Mg./100 Cc.*
0 to 0.5	20	2 to 14	3 to 6 (15)	4 (5)
0.51 to 0.74	17	2 to 16	5 to 10 (13)	6 (3); 7 (3)
0.75 to 0.99	26	3 to 13	7 to 10 (20)	9 (6); 10 (6)
1.00 to 1.49	51	2 to 28	7 to 14 (37)	10 (8)
1.50 to 1.99	28	4 to 26	7 to 12 (20)	11 (6)
2.00 to 2.49	15	5 to 22	.....	9 (3); 17 (2); 20 (2)
2.50 to 3.00	5	14 to 26	.....	14 (1); 15 (1); 17 (1); 22 (1); 26 (1)

* The figures in parentheses indicate the number of levels.

† The mode is the item in a series of statistical data that occurs oftenest.

INTERESTING BLOOD LEVELS

The following interesting blood levels were obtained and give a hint as to the rectal absorption of sulfadiazine and its slow excretion from the blood:

1. Low levels
   - (*a*) 1.2 mg. per hundred cubic centimeters forty-eight hours after administration of sulfadiazine had been stopped.
   - (*b*) 1.4 mg. per hundred cubic centimeters twenty-four hours after administration of sulfadiazine had been stopped.
   - (*c*) 2.2 mg. per hundred cubic centimeters eighteen hours after administration of sulfadiazine had been stopped.
   - (*d*) 1.8 mg. per hundred cubic centimeters after 15 Gm. of sulfadiazine had been given rectally in the previous twenty-four hours.
2. High levels
   - (*a*) 28.0 mg. per hundred cubic centimeters in a patient with streptococcic meningitis; subsequently the urine was packed with red blood cells, but it cleared when the use of the drug was stopped.
   - (*b*) 26.8 mg. per hundred cubic centimeters in a patient with meningococcic meningitis; later the urine was half packed with red blood cells, and oliguria, azotemia and ureteral obstruction developed, which eventually cleared.

CORRELATION OF TWENTY-FOUR HOUR DOSAGE AND BLOOD LEVELS

The blood levels reviewed were correlated with the previous twenty-four hour doses; these doses were calculated as grains per pound of body weight per twenty-four hours. Table 2 shows the results of this correlation; it gives the doses in grains per pound per twenty-four hours, the blood levels resulting and the average blood level for this dosage. A total of 162 levels was correlated.

SPINAL FLUID LEVELS

In the series of cases of meningitis, a total of 18 spinal fluid levels of sulfadiazine were determined. Almost simultaneously blood levels of sulfadiazine were also determined. The following correlations were made between the spinal fluid levels and the corresponding blood levels:

1. Six spinal fluid levels were half as high as the blood levels.
2. Five spinal fluid levels were two-thirds as high as the blood levels.
3. Two spinal fluid levels were three-fourths as high as the blood levels.
4. Five spinal fluid levels were four-fifths as high as the blood levels.

TOXIC EFFECTS

As stated previously, the toxic effects were most difficult to evaluate in children, especially any subjective effects. As far as we could tell, there was no difficulty with nausea or vomiting due to the drug. In no case was nausea or vomiting any greater than that ordinarily associated with the disease treated; and in no case was the use of sulfadiazine discontinued because of nausea or vomiting.

The other objective and subjective toxic effects are cited in the following summary, with the number of patients involved and the percentage of the total number of patients.

1. Urine
   - (*a*) Sulfadiazine crystals in urine but no red blood cells; condition cleared when dose was lowered—8 patients (9 per cent).
   - (*b*) Red blood cells in urine but no crystals; condition cleared when dose was lowered—12 patients (13 per cent).
   - (*c*) Crystals and red blood cells in urine, which cleared when dose was lowered—18 patients (20 per cent); also (1) pneumococcic meningitis till death and (2) tuberculous meningitis till death.
   - (*d*) Red blood cells and casts in urine on admission, which cleared during treatment with sulfadiazine—2 patients (2 per cent).
2. Blood
   - (*a*) Leukopenia (count less than 6,500)—25 patients (27 per cent).
   - (*b*) Neutropenia (count less than 20 per cent)—9 patients (10 per cent).
   - (*c*) Anemia (drop of 2 Gm. in hemoglobin content)—1 patient (1 per cent).
3. Skin
   - (*a*) Transitory questionable rash—2 patients (2 per cent).
4. Nervous system
   - (*a*) Transitory questionable neuritis—1 patient (1 per cent).
   - (*b*) Transitory questionable psychosis—1 patient (1 per cent).

COMMENT

From this review of 90 children receiving sulfadiazine and from the clinical observations while using the drug, the following comments seem justified.

1. Blood Levels.—For some reason, oral doses of sulfadiazine which should maintain adequate blood levels usually produce low levels at the end of the first twenty-four hours. This has been explained in some papers [8] on the basis of slow absorption. However, if the same dose is maintained, higher and adequate blood levels will be found usually in forty-eight hours. This original low level, of course, can be overcome by giving a larger initial dose or repeating the initial dose every hour for two or three hours. Once an adequate blood level is obtained, it is easily maintained. This has been explained on the basis of slow excretion,[8] and because of this, sulfadiazine may be given at greater intervals after the acute process has subsided. This was demonstrated very well in our cases of acute osteomyelitis without surgical intervention. After the temperature and the pulse had been brought under control, they were maintained normal by only relatively small doses of sulfadiazine every six hours and even every eight hours. This slowness of excretion was also shown by the blood levels obtained as late as eighteen hours, twenty-four hours and even forty-eight hours after the drug was discontinued. The absorption of sulfadiazine into the blood stream when administered rectally was poor.

When oral doses of sulfadiazine given to children exceeded 2 grains per pound (0.24 Gm. per kilogram) per twenty-four hours, it was impossible to predict the blood level. Oral doses of 1 to 1½ grains per pound (0.12 to 0.18 Gm. per kilogram) per twenty-four hours in 37 of 51 instances produced blood levels of 7 to 14 mg. of free sulfadiazine per hundred cubic centimeters, and 8 of these levels were 10 mg. Oral doses of ¾ to 1 grain per pound (0.09 to 0.12 Gm. per kilogram) per twenty-four hours gave the most consistently adequate blood levels; 20 out of 26 were between 7 and 10 mg. per hundred cubic centimeters and 12 of these were between 9 and 10 mg.

Aside from the weight, the state of hydration or fluid intake had the greatest effect on the blood levels. With poor fluid intake an ordinary dose of sulfadiazine would produce high blood levels and a marked increase in the toxic renal reactions.

2. Spinal Fluid Levels.—In the series of 18 spinal fluids, the sulfadiazine levels were found to be consistently high. All were at least half as high as the blood level, and two thirds of the spinal fluid levels were found to be two thirds as high as the blood levels or higher. Because of this, the use of sulfadiazine is of distinct advantage in the treatment of the various meningitides. From our experience, we feel that in practically all types of bacterial meningitis, except tuberculous, sulfadiazine is the drug of choice. We also believe that if meningitis can be diagnosed and treated as early as possible with sulfadiazine—and in some cases with recognized supportive measures, such as specific antiserums—better results will be obtained than have ever been reported previously. The longer diagnosis is delayed, with the formation of a thicker, more purulent and fibrinous spinal fluid, the less chance there is of a normal recovery even with sulfadiazine.

3. Toxic Effects.—This review reveals toxic effects of sulfadiazine to be greater than those previously reported, but to be no different than those commonly seen with other sulfonamide compounds. We found little or no nausea or vomiting due

8. Billings, F. T., Jr., and Wood, W. B., Jr.: Studies on Sulfadiazine, Bull. Johns Hopkins Hosp. **69**:314 (Oct.) 1941. Trevott, G. I.; Nelson, R. A., and Long, P. H.: Studies on Sulfadiazine, ibid. **69**:303 (Oct.) 1941.

to the drug. We found only one questionable cutaneous rash and only two questionable reactions in the central nervous system; for all of these children we discontinued the use of the drug immediately, because they were not severely ill.

However, in 27 per cent of our patients receiving sulfadiazine a white blood cell count of less than 6,500 developed, and 10 per cent of our patients had a drop in neutrophils to less than 20 per cent. Most of the patients with leukopenia responded to lowering the dosage of the drug, but those with neutropenia responded only to discontinuing the drug. If the leukocyte count continued to become lower or if the neutrophils went below 10 per cent we gave the patients a prophylactic blood transfusion. There were no critical or fatal reactions observed from this procedure. There was only 1 patient who seemed to have a questionable direct drop in hemoglobin content due to the administration of sulfadiazine.

The greatest evidence of toxicity was found in the urinary system. We found 41 patients of 90, or 45 per cent, with crystals alone, with red blood cells alone or with both on urinalysis. These abnormalities were apparently due indirectly to too great a concentration of sulfadiazine in the blood, because they promptly cleared when the dose of sulfadiazine was lowered or use of the drug was discontinued and when the intake of fluid was increased. We had 1 patient, described earlier in this paper, in whom oliguria, azotemia and left ureteral obstruction developed, which cleared after cystoscopy and the administration of fluids parenterally.

As mentioned before, earlier papers have not reported this high incidence of urinary reactions and tend to prove sulfadiazine relatively nontoxic. However, Murphy and his associates [9] at the Milwaukee County General Hospital (unpublished data on adults) have also found a large number of patients who had crystals, hematuria and urinary suppression following use of sulfadiazine. More recent articles [10] have also called attention to this complication.

We feel that there are two reasons for our high incidence of urinary reactions:

1. We had no standardized dosage table for children during this study. In view of the observed blood levels, we feel that we administered too large a dose to most of the children, which was readjusted after laboratory observations were reported.

2. The fluid intake of sick infants and children is difficult to maintain, and because of poor fluid intake and moderate dehydration, many of the children acquired high concentrations of the drug in the blood, kidneys and urine. This seems to be borne out by the fact that nearly all urinary reactions cleared after mere lowering of the dose and forcing of fluids by mouth or giving of fluids parenterally. An excellent example of this is found in one of our cases of acute osteomyelitis without surgical intervention. The patient weighed only 51 pounds (23.1 Kg.) but because of the severity of the process received large doses of sulfadiazine orally, 1 Gm. every four hours. Ordinarily, with poor fluid intake, this patient would have shown high blood levels, crystals and hematuria in several days. However, without much encouragement he took approximately 3,500 to

9. Murphy, F. D.: Personal communication to the authors.

10. Thompson, G. J.; Perrell, W. E., and Brown, A. E.: Anuria After Sulfadiazine Therapy, Proc. Staff Meet., Mayo Clin. **16**:609 (Sept. 24) 1941. Gross, P.; Cooper, P. B., and Hagon, M. L.: Urolithiasis Medicamentosa Caused by Sulfadiazine, Am. J. Clin. Path. **11**:882 (Dec.) 1941. Bradford, H. A., and Shaffer, J. H.: Renal Changes in a Case of Sulfadiazine Anuria, J. A. M. A. **119**:316 (May 23) 1942. Schulte, J. W.; Schidler, F. P., and Niebauer, J. J.: Acute Urinary Suppression Following Sulfadiazine Therapy, ibid. **119**:411 (May 30) 1942. Raines, L. R.: Ureteral Obstruction Following Use of Sulfadiazine, ibid. **119**:427 (June 6) 1942. Hellwig, C. A., and Reed, H. L.: Fatal Anureaia Following Sulfadiazine Therapy, ibid. **119**:561 (June 13) 1942.

4,000 cc. of fluids a day for nearly seven days. We believe that because of this fact alone he did not manifest any urinary reactions, and we had difficulty maintaining his blood level between 8 and 10 mg. per hundred cubic centimeters. His recovery has been described.

4. Sodium Sulfadiazine.—This product was used little during the regular study because of the ease with which orally administered sulfadiazine was tolerated, even by the patients with meningitis. However, we have used more of it recently with satisfactory results. We have used it only intravenously and in amounts of ⅓ grain per pound (0.04 Gm. per kilogram) per dose. This is made into a 5 per cent solution with distilled water. We have repeated it at either twelve hour or eight hour intervals, depending on the blood levels obtained and the response of the disease. After seeing several patients respond well with the use of sodium sulfadiazine intravenously, we believe that it would be a distinct advantage in cases of severe infection to use an initial intravenous dose of sodium sulfadiazine, supplemented by oral doses of sulfadiazine to produce an immediately adequate blood level.

5. Sulfadiazine Spray for Burns.—Three per cent of sulfadiazine in 8 per cent triethanolamine to be used for the treatment of burns was also supplied [1] and has been used on 12 patients to date. No attempt will be made here to evaluate its use or the results obtained. We can state that on most patients it produces a thin, pliable eschar; that it keeps the burned areas clean and surprisingly free from infection, and that when burns are extensive considerable amounts of sulfadiazine may be absorbed into the blood. As an example of the latter, we have 1 patient with an estimated 13 per cent of body surface having first, second and third degree burns who had a blood level of 7.8 mg. per hundred cubic centimeters after receiving the spray every hour for the first twenty-four hours and who had red blood cells in the urine on the second day of spraying.

CONCLUSIONS

High blood levels are easily reached and maintained with sulfadiazine because of relatively slow excretion; because of this, sulfadiazine may be given at greater intervals or in smaller doses.

Sulfadiazine given in doses of ¾ to 1 grain per pound per twenty-four hours to children will produce an average blood level of 7 to 10 mg. per hundred cubic centimeters, which is adequate for usual infections.

Sulfadiazine is effective against most of the common bacteria producing specific infections, especially hemolytic streptococci, pneumococci, Staph. aureus haemolyticus, meningococci and H. influenzae.

Sulfadiazine passes readily into the spinal fluid, and spinal fluid levels can usually be expected to be two thirds or more of the blood level.

With high blood levels or poor intake of fluids, the most common reactions are crystals in the urine, red blood cells in the urine, leukopenia and neutropenia, which seem to clear when the administration of the drug is stopped.

Sulfadiazine spray for burns produces a satisfactory eschar and is effective in preventing secondary infection.

Patients receiving sulfadiazine should be observed with the same care that is advisable after administration of any other sulfonamide compound, and the urine and the blood count should be checked regularly with continued administration.

STUDIES ON VITAMIN A

VITAMIN A AND TOTAL LIPID OF THE SERUM IN PNEUMONIA

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The relationship between vitamin A and carotene of the serum and the lipids of the serum has been stressed in previous communications.[1] From the literature it is evident that the vitamin A and the lipids of the serum behave similarly during the course of pneumonia and during convalescence. Thus, it is known that during the course of pneumonia the vitamin A of the serum is reduced sometimes to an extreme degree, though complete absence is rare.[2] Likewise during infections the lipids may be reduced and, as in the case of vitamin A, the reduction is likely to be especially great in pneumonia.[3] There is some disagreement concerning the level of vitamin A storage in pneumonia, certain investigators claiming to have found a reduction, though usually it was rather slight,[4] and others having found none.[5] However, it is evident from the published figures that the loss during the acute process is not great enough ordinarily to be a factor in the reduction of the blood level of the vitamin or to lead to a dangerous degree of depletion except in rare instances.[5a]

Observers have noted the rapid return of the vitamin A to normal values during convalescence from pneumonia and have commented on the fact that in many cases a rise to above the average normal level occurred.[2] Likewise, in the case of the lipids there has been found a rapid rise to normal as soon as the temperature fell.[3a, b] Moreover, Steiner and Turner [3c] found that the serum cholesterol tended to rise to a point well above the normal and to remain at a high level for a considerable time.

The mechanism of the fall and subsequent rise of vitamin A has not yet received adequate investigation. From published figures, it is evident that a reduction of

From the Department of Pediatrics of the John Hopkins University School of Medicine and the Harriet Lane Home of the Johns Hopkins Hospital.

1. Josephs, H. W.: Bull. Johns Hopkins Hosp. (*a*) **65**:112, 1939; (*b*) **71**:253 and 265, 1942.

2. (*a*) Lindqvist, T.: Acta med. Scandinav. (supp.) **97**:15, 1938. (*b*) Clausen, S. W., and McCoord, A. B.: J. Pediat. **13**:635, 1938. (*c*) May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. J., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 (June) 1940. (*d*) Thiele, W., and Scherf, J.: Klin. Wchnschr. **18**:1275, 1939.

3. (*a*) Stoesser, A. V., and McQuarrie, I.: Influence of Acute Infection and Artificial Fever on Plasma Lipids, Am. J. Dis. Child. **49**:658 (March) 1935. (*b*) Stoesser, A. V.: Altered Lipid Metabolism in Acute Infections of Infants and of Older Children, ibid. **56**:1215 (Dec.) 1938. (*c*) Steiner, A., and Turner, K. B.: J. Clin. Investigation **19**:373, 1940.

4. Moore, T.: Lancet **2**:669, 1932; Biochem J. **31**:155, 1937. Fox, F. W.: Lancet **1**: 953, 1933. Ralli, E. P.; Papper, E.; Paley, K., and Baumann, E.: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects, Arch. Int. Med. **68**:102 (July) 1941.

5. Breusch, A., and Scalabrino, R.: Ztschr. f. d. ges. exper. Med. **94**:569, 1934. Wolff, L. K.: Lancet **2**:617, 1932. Lindqvist.[2a]

5a. These statements are based on averages of large numbers of extremely divergent figures. For this reason the statement that vitamin A is or is not reduced in pneumonia can be used only in a general sense and cannot be applied in individual cases. In any series there are many low figures, more than one would find in an equivalent normal series. Because of this greater number of low figures in pneumonia, I have been inclined to the belief that the reduction in vitamin A stores in pneumonia is a factor of importance in the interpretation of findings.

the stores from which the vitamin A of the serum may be drawn is not a factor. Excretion in the urine in pneumonia has been found to occur by many observers, and Moore [6] has recently studied the phenomenon and suggested that the amount of excretion, which may at times be high, may account for the reduction of vitamin A in the serum. However, the excretion is variable in pneumonia, and from the figures in Lindqvist's article no correlation is found between urinary excretion and values for serum vitamin A. It has been suggested that the increased metabolic rate during infection makes extra demands on the utilization of vitamin A or may cause its destruction. Support for this hypothesis is found in the fact that thyroxin causes a reduction of the vitamin A content of the blood. It must, however, be noted that not all infections have the great effect on serum vitamin A levels that pneumonia has and that the body temperature, although an important factor as shown by observations on induced malaria,[2c, d] is variable in its effect. Lindqvist investigated the lungs after death from pneumonia and found no increase in vitamin A content. The possibility that vitamin A may be destroyed in the involved areas of the lungs has, however, not been excluded. Figures of Stoesser [3b] on lipid partitions and iodine numbers suggest that functional damage of the liver may be a factor at least in the lipid variations. Studies on the partition of urobilin between stools and urine (unpublished) suggest that in most if not all cases of pneumonia there is some disturbance in hepatic function, and it is not at all unlikely that such a disturbance may have a bearing on the variations in the serum vitamin A.

From all this evidence one gains the realization that there are a number of more or less isolated facts but no knowledge of relationships that might explain the known phenomena. The one relationship that stands out is the similarity in the behavior of the vitamin A and the lipids of the serum: (1) the rapid fall in pneumonia; (2) the rapid rise in convalescence, often to a point above the normal, and (3) the fact that this relationship appears to be a widespread occurrence, not confined to pneumonia, and so probably of more or less fundamental significance. The purpose of this work, therefore, is to study the relationship between vitamin A, carotene and lipids in pneumonia and during convalescence in the hope of learning something that will throw some light on the mechanism of the changes that are known to occur.

PLAN OF STUDY AND METHODS

The plan of study was to make simultaneous determinations of vitamin A, carotene and total lipids on the serum of blood drawn at frequent intervals during pneumonia and during convalescence. These figures were to be correlated with such factors as severity of the pneumonic process, duration of the disease, height of the fever, previous diet and age of the patient. Also to be studied was the effect of vitamin A and carotene given at various levels during pneumonia and convalescence to determine both the postabsorptive blood levels and the effect on the blood lipids, as was done in a recent study on rats.

The blood was obtained either by venipuncture or by drawing it from a deep stab in the heel, the latter method proving the more satisfactory, since there was a smaller incidence of hemolysis. The methods used for determining vitamin A, carotene and total lipids have been described in a previous communication.[1a] The children studied were in the pneumonia wards of the Harriet Lane Home and because of the need for beds could not be kept for study for more than a short time after they were convalescent. Vitamin A supplement was given as percomorph liver oil (0.5 cc.) or halibut liver oil (2 cc.), the latter being used when it was desired to give a larger dose of vitamin A without giving an excessive amount of vitamin D. Five or 10 cc. of carotene in oil (4.5 mg. of the provitamin per cubic centimeter) was given daily over a period of five days. From the appearance of the stools it is evident that much was unabsorbed.

6. Lawrie, N. R.; Moore, T., and Rajagopal, K. R.: Biochem. J. **35**:825, 1941.

RESULTS

The results will be presented in three parts:

I. The values for total lipid, carotene and vitamin A during the course of pneumonia. The patients are divided into three age groups: (1) over 2 years; (2) 1 to 2 years, and (3) under 1 year.

II. The values for total lipid, carotene and vitamin A during convalescence. As far as possible several figures were obtained for each patient so that the individual course can be charted. It must of course be realized that the necessity for discharging patients as soon as they were well made it impossible to carry the study along for more than about ten days to two weeks. The age groups were the same, except that it was found desirable to subdivide the group under a year of age into two parts: (1) infants 8 months to 1 year old and (2) infants under 8 months old.

III. The relationships between lipid levels and vitamin A and carotene. In this part results for infants over a year old and those for infants under a year old

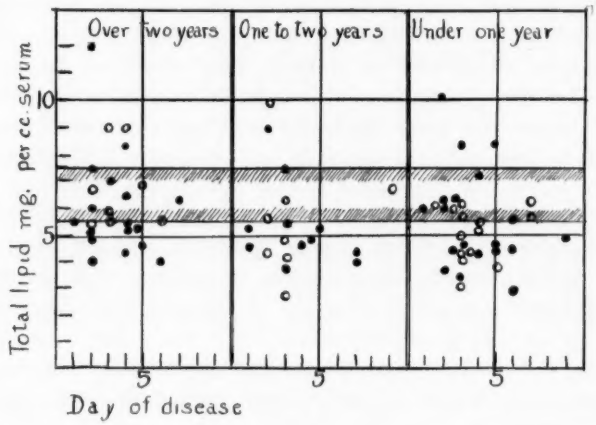

Chart 1.—Total lipid of the serum during the course of pneumonia. The solid circles represent patients whose temperature was 40 C. (104 F.) or above. The hollow circles represent patients with temperatures below 40 C. The space between the shaded lines represents the approximate limits of the great majority of normal values.

are analyzed together. Finally the relation of lipid levels to the so-called "post-absorptive curves" of vitamin A is charted.

I. During Pneumonia.—The total lipid (chart 1) was in general reduced during the course of pneumonia. The reduction, however, seems to follow no rule except that the high values present in the first few days of the disease become less and less frequent in the prolongation of the period of fever. However, extremely low values are present as early as the second day. Among the older children those with temperatures above 40 C. (104 F.) appear to have definitely lower lipid values than those with temperatures below 40 C. On the other hand, in the younger children no correlation between temperature and lipid values existed. In the light of Stoesser and McQuarrie's [3a] observation that fever per se has no influence on lipid values, this difference probably means no more than that fever is a more reliable indicator of severity of the process in older than in younger children. Another difference related to age is that lipid values are reduced to a greater extent in children under 2 years of age. This greater reduction is probably related to

the fact that the general lipid level in infancy is somewhat lower than in later childhood (personal observation), but one cannot exclude the possibility of a greater lability in serum lipid levels similar to the greater lability in other physiologic functions, which is one of the outstanding characteristics of infancy. Previous diet appears to have no influence on the lipid levels in pneumonia.

In the case of carotene (chart 2), the reduction progresses fairly regularly with the duration of the disease. The preponderance of low values in the patients under 1 year of age is no more than would be expected from the diet, which at this age is not likely to contain carotenoids in more than small amounts.

The reduction in vitamin A (chart 3) is striking and is present from the outset. In the patients with high fever there is practically no difference that can be attributed to age. In the group under a year old, however, infants with lower

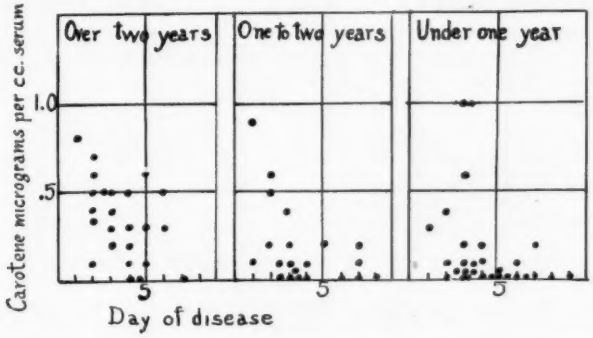

Chart 2.—Carotene of the serum during the course of pneumonia.

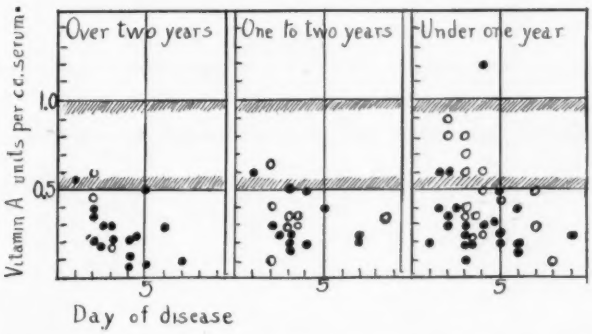

Chart 3.—Vitamin A of the serum during the course of pneumonia. The symbols have the same meaning as in chart 1.

temperatures appear to have less reduction in vitamin A than those with higher temperatures. There are too few figures from patients with lower temperatures in the upper age groups to allow any definite statement, but from the literature it is evident that the temperature is an important factor in the reduction of vitamin A, in contrast to its effect on lipids,[2] and also that the effect of rise in temperature may be extraordinarily rapid.[2d]

The only effect of the previous diet on vitamin A or carotene that could be demonstrated was that a rather poor diet had been taken by those patients in whom early in the pneumonia the carotene was found absent or greatly reduced. The effect of a deficient diet on vitamin A levels of course is not excluded, for the rapidity with which vitamin A is reduced by the infection would obscure any other influence to such a degree that it would be difficult to demonstrate it.

II. During Convalescence.—As soon as the temperature falls, the lipid shows a tendency to rise, as was pointed out in the introduction. This rise, however, is related to age, as may be seen from chart 4. In the patients over 2 years of age, the rise was marked; not only did almost all of them eventually show levels above the upper limits of normal, but there was little tendency during the period of observation to return to normal values (Steiner and Turner [3c]). In the age group from 1 to 2 years and in that from 8 to 12 months this tendency is still present but considerably less in extent and by the end of two weeks almost all the lipid values have returned to normal limits. In the group under 8 months the tendency for the lipids to rise above normal levels is absent. The exceptional cases will be discussed in a later portion of this paper.

The carotene rose as would be expected during convalescence (chart 5). Two facts are of interest in relation to carotene levels: (1) The patients from 8 to

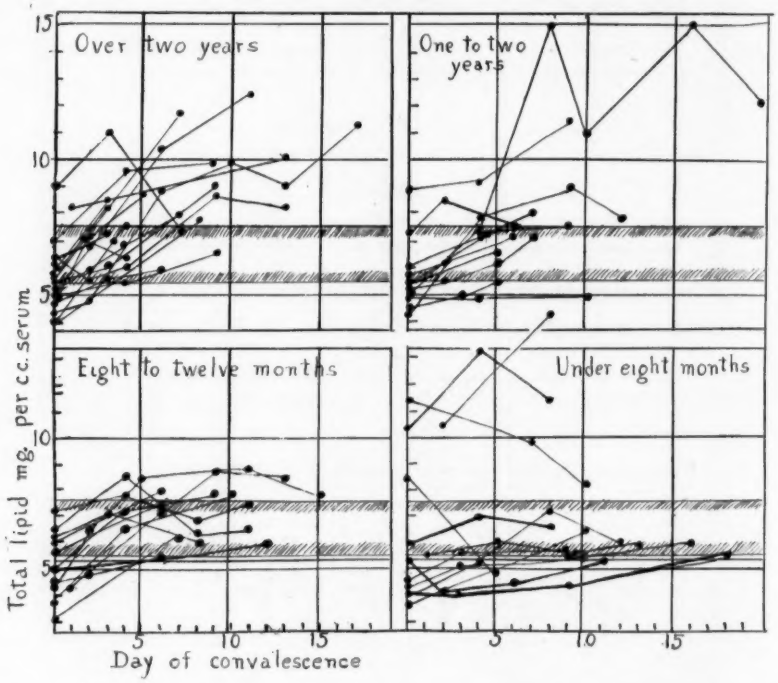

Chart 4.—Total lipid of the serum during convalescence from pneumonia (no vitamin A supplement).

12 months receiving vitamin A acquired rather higher carotene levels than those not receiving vitamin A; (2) the administration of carotene to the patients of 8 to 12 months resulted, as should be expected, in higher serum carotene levels in most. On the other hand, in the group under 8 months of age ingestion of carotene had no influence on serum levels. The reason for these peculiarities will be discussed later.

The changes in vitamin A are seen in chart 6. The difference in response at different ages is evident. It is impossible to say whether there is any significance in the fact that slightly higher values were obtained in the group under 8 months than in the group from 8 to 12 months.

Influence of the Administration of Vitamin A: When vitamin A was given daily to the patients under 2 years of age during convalescence, the effect was to produce

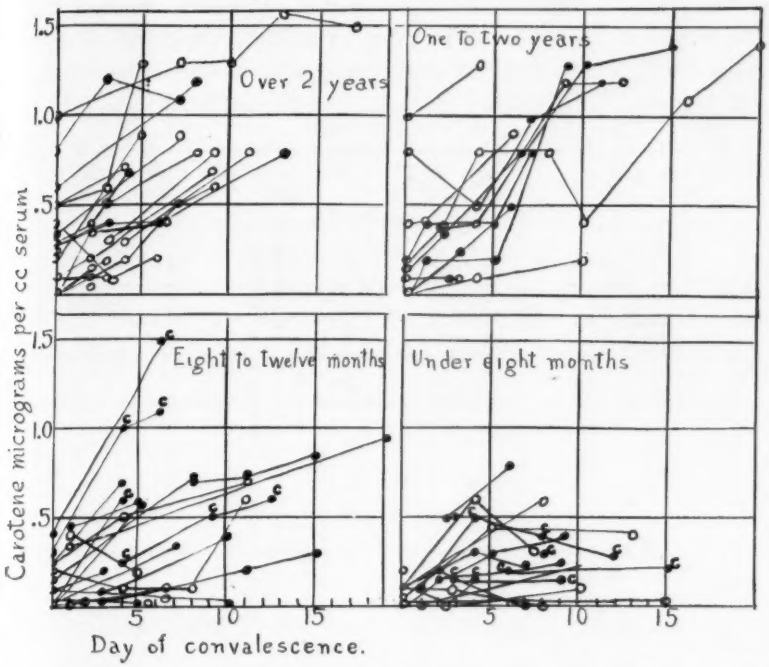

Chart 5.—**Carotene of serum during convalescence from pneumonia. The hollow circles represent patients not receiving any vitamin A supplement. The solid circles represent patients receiving vitamin A supplement. The solid circles marked *C* represent patients receiving carotene.**

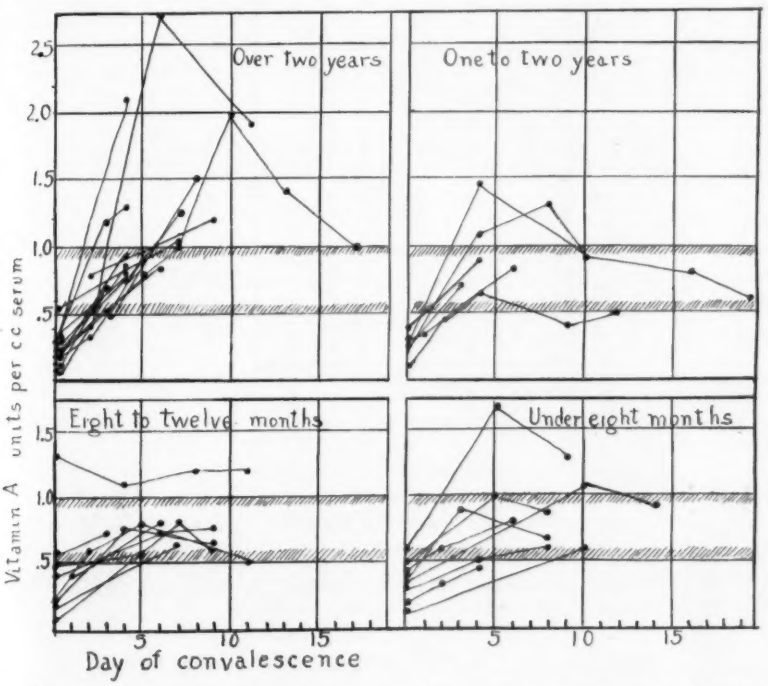

Chart 6.—**Vitamin A of serum during convalescence from pneumonia (no vitamin A supplement).**

a lipid response similar to that in the older group, who had received no vitamin A, except that it was not so prolonged (chart 7). Also, as previously pointed out in the discussion of chart 4, the effect in the age group under 8 months was much less than in the others. The vitamin A was given at two levels: 0.5 cc. of perco-

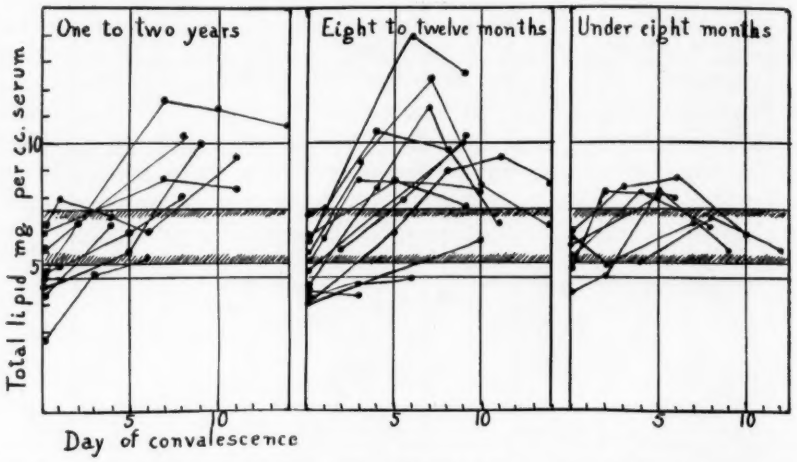

Chart 7.—Total lipid of the serum during convalescence from pneumonia (patients receiving vitamin A supplement).

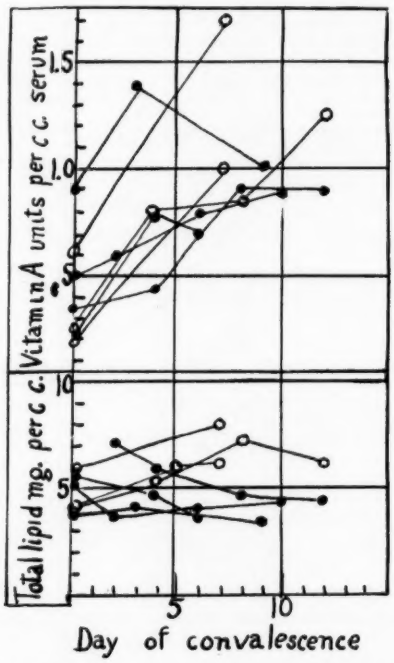

Chart 8.—Vitamin A and total lipid of serum during convalescence from pneumonia (patients under 1 year of age receiving carotene). The solid circles represent patients receiving 10 cc. of carotene in oil; the hollow circles, patients receiving 5 cc.

morph liver oil, corresponding to about 20,000 to 25,000 U. S. P. units of the vitamin a day, and (2) 2 cc. of halibut liver oil (to avoid giving excessive vitamin D), corresponding to 80,000 to 100,000 U. S. P. units of the vitamin a day. No

striking difference in the effects of the two doses was seen. If anything, the larger dose produced slightly less effect.

The influence of vitamin A on the lipid curves is of the utmost importance, for it indicates that vitamin A exerts a physiologic influence on lipid metabolism. The same type of effect has been shown to occur in rats, especially those previously made deficient in vitamin A.[1b] This will be discussed later.

Effect of Ingestion of Carotene: It was expected that the carotene, which was given at a fairly high dosage, would resemble vitamin A in its effect. The results were, however, surprising (chart 8). When given at a level of 5 cc. (22 mg., corresponding to 35,000 U. S. P. units of vitamin A) the effect on lipids was nil, while the rise in vitamin A was somewhat greater than occurred in infants of the same age group given no supplement. When given at a level of 10 cc., there occurred an actual fall in lipid level or if the level was already low there was no

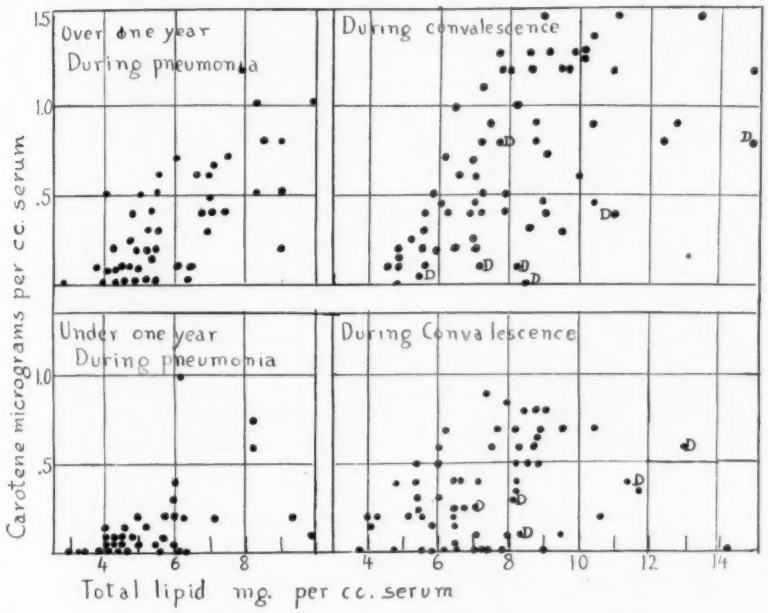

Chart 9.—Relationship of carotene to total lipids of the serum during pneumonia and convalescence. Note: The points marked *D* represent patients whose diet previous to admission was judged to have been deficient in carotenoids. Under a year of age it was virtually impossible to make the distinction.

tendency to rise. The vitamin A, on the other hand, rose, though not quite as well as in the case of the smaller dose of carotene. No explanation for these results is offered.

III. Influence of Lipid Levels.—Chart 9 shows the relationship of carotene and lipids of the serum. The correlation is relatively high, considering the difficulty of controlling the previous diet. In the children over 1 year of age, the carotene content of whose diet is higher than that of infants under 1 year of age, the effect of a diet estimated to be deficient in carotenoids is clear (points marked *D* in the chart). For the lower age group, low intake of carotene is the rule, even though the diet may be adequate in other respects, including vitamin A, so that it is not surprising to find low values for serum carotene even with diets classified as good. For this reason it is felt that it is the left border of the curve that is of significance in establishing a correlation. It is interesting that this border is virtually the same

for the figures obtained during the acute stage of pneumonia as for those obtained during convalescence. This indicates the importance of the lipid levels in determining carotene levels and suggests that the infection influences the carotene largely by means of its effect on lipids. It may be recalled that the infants from 8 to 12 months of age receiving vitamin A had in general higher serum carotene values than those not receiving vitamin A, whereas this was not true of those below 8 months of age. This difference between the two groups may be explained by the effect of serum lipids on serum carotene, since administration of vitamin A was accompanied by a rise in lipids in the patients between 8 and 12 months but not in the younger group. In a study of hypothyroidism (to be published) it was likewise concluded that the serum carotene levels were determined largely by the lipid levels.

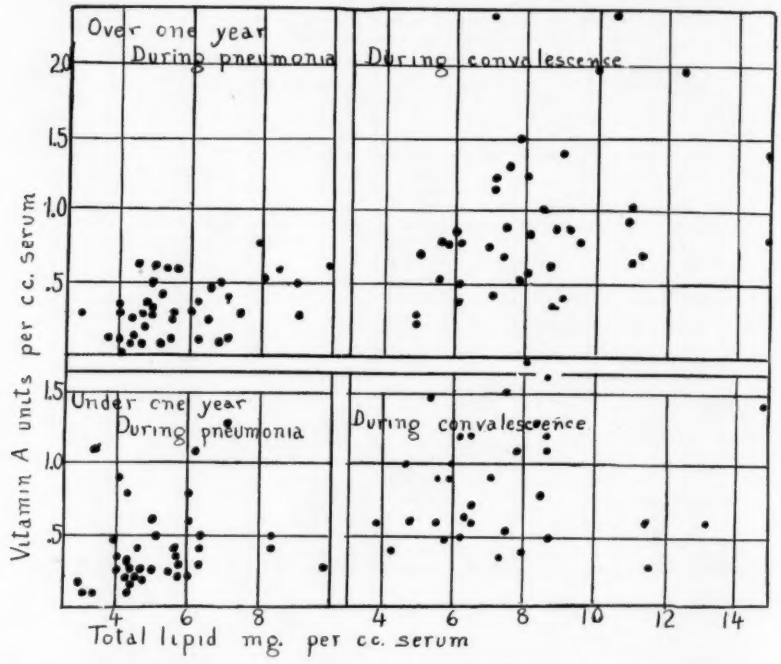

Chart 10.—Relationship between vitamin A and total lipids of the serum during pneumonia and convalescence.

For vitamin A the results are quite different (chart 10). During pneumonia there is no correlation. During convalescence the correlation is low. The only relationship that exists is that with a few exceptions those patients that showed a marked rise in lipid values showed also a marked rise in vitamin A, and those that had little rise of lipid level had also little rise of vitamin A level. In the individual cases, however, the peak of the lipid curve did not always coincide with that of the vitamin A curve. Usually the vitamin A values had reached their peak and were already beginning to decline while the lipid values were still increasing (charts 13 and 14). All this suggests that what correlation there is exists because the vitamin A and the lipids of the serum are subject to similar influences to which they react with different degrees of lability and that the solubility of vitamin A in the lipids is of less importance. In other words, the problem is the mobilization of vitamin A from its stores, and in this the solubility in the lipids plays a minor role.

Influence of Lipid Level on Absorption of Vitamin A and Carotene: The serum lipid level is apparently of more importance as a factor in the absorption of vitamin A from the intestines. In chart 11 the vitamin A content of the serum four to six hours after ingestion of halibut liver oil or percomorph liver oil is correlated with the lipid level. Here the influence of the lipid level is clear, and the presence of pneumonia makes no demonstrable difference. The same influence is apparently present also in the case of absorption of carotene (chart 12), though

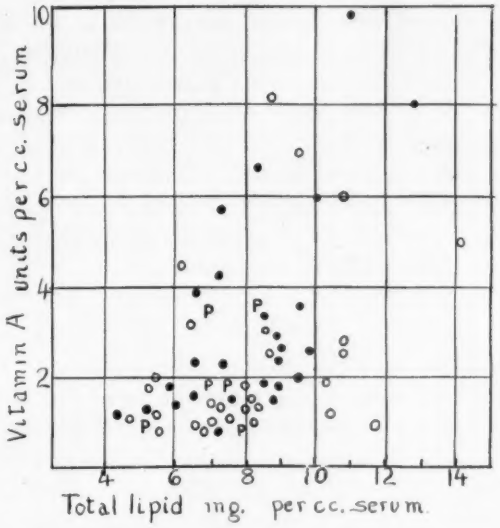

Chart 11.—Relationship of total lipid of the serum to the vitamin A of the serum four to six hours after ingestion of a vitamin A concentrate. The solid circles represent patients receiving 2 cc. of halibut liver oil; the hollow circles, patients receiving 0.5 cc. of percomorph liver oil. *P* represents patients on whom the determinations were made during the acute stage of pneumonia.

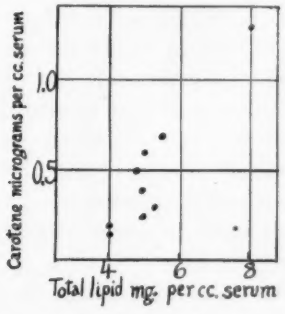

Chart 12.—Relationship between total lipid and carotene of the serum of patients receiving supplements of carotene in oil.

the number of values is small and the method of determining the relationship is open to criticism.[7] The correlation between serum lipids and the absorption curves of vitamin A and carotene serves to explain certain observations that have been

7. While the level of ingestion of carotene is of the utmost importance as a factor in the blood level, the effect of ingested carotene is only slowly realized, so that it takes four or five days for increased ingestion to be fully reflected by the increase in serum levels. During this time changes in lipid level are occurring. To obtain a correlation, the serum carotene level four to five days after ingestion of carotene was begun was charted against the probable average serum lipid level during this five day period.

reported from time to time. Thus Clausen's finding [2b] that vitamin A is less well absorbed in pneumonia receives a probable explanation in the low lipid levels of pneumonia. Likewise, reduction in absorption of carotene in infections, especially commented on by Clausen [2b] and by Heymann,[8] may be similarly explained. It may also be recalled that the ingestion of carotene produced higher serum carotene values in the infants 8 to 12 months of age than in those under 8 months. The difference in lipid response between these two groups is evidently the primary factor.

Exceptional Cases.—There were certain exceptions to the general statements made concerning the behavior of the serum lipids and of vitamin A. In some cases high lipid values were found to occur during pneumonia and to persist for a time into convalescence. In one or two other cases the level of vitamin A was inexplicably high. No explanation is offered for such behavior; such exceptions merely emphasize the fact that there must be factors influencing the lipid and the vitamin A levels which investigators have not yet learned to recognize. Two of the exceptional values have in common the fact that the previous diet of the patient had been extremely deficient. These will be discussed later.

COMMENT

The results recorded here confirm those of others in regard to the behavior of vitamin A, carotene and total lipid of the serum in pneumonia as presented in the introduction. The problem of mechanism remains to be discussed. It is reasonably certain that the serum carotene levels are largely determined by the serum lipid levels as well as by the carotene intake, due allowance being made for a certain sluggishness of response to carotene (charts 13 and 14). Vitamin A levels, on the other hand, are not determined by the lipid levels during pneumonia, and yet one cannot escape the fact that they act in a similar manner both during and after pneumonia and that therefore there may be a relationship. Of the various hypotheses presented in the introduction to explain the reduction of vitamin A, two appear most likely: (1) that vitamin A is withdrawn at an increased rate from the blood to supply the increased demands of tissue metabolism; (2) that the infection introduces factors that inhibit the mobilization of vitamin A.

The first of these two possibilities depends on (1) the demonstration of a reduction of the vitamin A reserves, which is greater the longer the duration of the infection; (2) the fact that, in general, infections are accompanied by increased utilization or destruction of vitamins, vitamin C and D being notable examples, and (3) the fact that hyperthyroidism is also accompanied by reduction of the vitamin A content of the blood,[9] and it has been presumed that thyroxin causes an increased rate of utilization or destruction.[10]

The reduction of vitamin A stores in pneumonia, though not marked when averages are considered, may be extreme in some cases and constitutes direct evidence that demands for vitamin A in pneumonia are increased. The inference, therefore, that this increased demand is a factor in the reduction of blood levels seems justified.

On the other hand, the reduction in stores is apparently a variable phenomenon and in most cases would not be sufficient to be recognized by the method that must be employed for the purpose. The reduction in serum vitamin A is, however,

8. Heymann, W.: Absorption of Carotene, Am. J. Dis. Child. **51**:273 (Feb.) 1936.

9. Wendt, H.: München. med. Wchnschr. **82**:1679, 1935. Clausen and McCoord.[2b]

10. Sure, B., and Buchanan, K. S.: J. Nutrition **13**:521, 1937. Abelin, I.; Knuchel, M., and Spichtin, W.: Biochem. Ztschr. **228**:189, 1930.

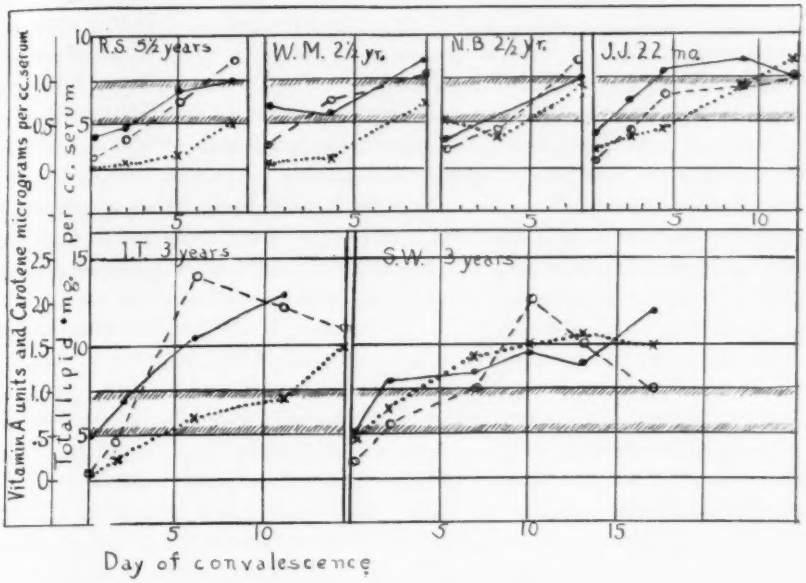
R.S. 5½ years
W. M. 2½ yr.
N.B 2½ yr.
J.J. 22 mo.
I.T. 3 years
S.W. 3 years
Vitamin A units and Carotene micrograms per cc. serum
Total lipid mg. per cc. serum
Day of convalescence

Chart 13.—Curves of serum vitamin A, total lipid and carotene for individual patients. This chart and the next are constructed in such a way that probable normal limits of vitamin A and total lipid correspond. This of course causes the base line for vitamin A and carotene to correspond to the line representing 2.5 mg. of lipid per cubic centimeter of serum. This chart and the next one are intended to illustrate the relationship between vitamin A, carotene and total lipid in individual patients, as mentioned from time to time in the text. They represent all the patients on whom observations were made far enough into convalescence to be of value for the purpose. The solid circles connected by a solid line represent total lipids; the hollow circles connected by a broken line represent vitamin A; the crosses connected by a dotted line represent carotene.

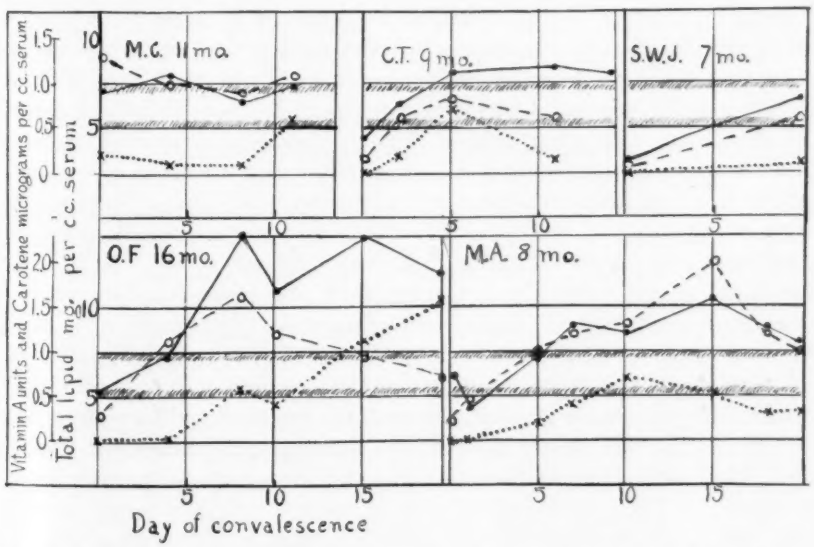
M.C. 11 mo.
C.T. 9 mo.
S.W.J. 7 mo.
O.F 16 mo.
M.A. 8 mo.
Vitamin A units and Carotene micrograms per cc. serum
Total lipid mg. per cc. serum
Day of convalescence

Chart 14.—Curves of serum vitamin A, total lipid and carotene for individual patients. The symbols have the same significance as in chart 13. O. F. and M. A. are patients specially discussed in the text and presumed to have some degree of vitamin A deficiency.

a practically constant phenomenon and judging by Lindqvist's figures is not related to probable loss of stores, which in his series of cases appears not to have occurred. This brings up the question of an inhibition of mobilization as a factor in the blood levels, but aside from a few isolated pieces of work nothing is known concerning the factors that influence such mobilization.

This is an important problem and may be stated simply as follows: Is vitamin A reduced because it is being taken out of the blood stream for use or destruction too rapidly or because it is being held back in stores? As has been said, there is evidence for both points of view. It seems likely that there is an actual tendency to increased destruction or utilization of vitamin A in pneumonia but that mobilization does not meet the demands. In this sense the failure to mobilize vitamin A can be looked on as a conservative process, an attempt, as it were, on the part of the organism to prevent depletion of an essential substance. The cases in which depletion of vitamin A has occurred are those in which this "protective" mechanism has failed.

Another problem of importance is the relation of the low vitamin A levels to the possible development of deficiency. There are two ways in which deficiency may be considered apart from the presence of characteristic anatomic lesions, which are admittedly late manifestations. One is the disappearance of stores of vitamin A, which in rats can progress to a considerable degree before the blood level begins to be affected.[1b] The other is a lowering of the blood level to a point at which adequate distribution to the tissues is interfered with. It is this second type of deficiency which is of concern here, since, as has been pointed out, in pneumonia the stores of vitamin A are significantly reduced only in a minority of patients.

It has been shown that visible manifestations of deficiency in rats can be prevented by a daily dose of vitamin A which is too small to cause detectable amounts of vitamin A to appear in the serum.[11] Likewise, in human beings one frequently finds extremely low serum values in association with various deficiencies but without any of the recognized characteristics of vitamin A deficiency except occasionally night blindness. It seems of doubtful expediency to consider a low serum vitamin A level per se as sufficient evidence of deficiency, for that is an avoidance of the fundamental problem by once and for all defining vitamin A deficiency on this basis. Sooner or later it may be able to do this, but until more is known of the conditions under which serum vitamin A is reduced it seems better to suspend judgment. In pneumonia, it does no good to say that of course there is deficiency because the serum level is low, when it is not known either how low the serum value can go before distribution to the tissues is seriously interfered with or how long a period can intervene before depletion of the vitamin in the tissues becomes serious as the result of the failure of distribution.

Recent work on rats may force a revision of the conceptions on the mechanism of deficiency. Baumann, Rüsing and Steenbock,[12] in order to explain the "latent" period between disappearance of vitamin A stores and development of the recognizable signs of deficiency, suggested that vitamin A might act to prevent certain toxic changes which in the absence of the vitamin are more directly responsible for the changes in the tissues. In a recent publication,[1b] it was shown that during development of deficiency in rats the total lipid of the serum is considerably reduced. Then, when vitamin A is given a reaction occurs which may have an important bearing on the changes occurring in pneumonia and during convalescence.

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11. Josephs[1b] has extensive references to the literature.
12. Baumann, C. A.; Rüsing, B. M., and Steenbock, H.: J. Biol. Chem. **107**:705, 1934.

This reaction consists of a rise in the serum lipids occurring when the rats are given a large daily dose of vitamin A. The lipids rise to a point above the normal and then fall back to normal limits while the excessive vitamin dosage is being continued. The reaction occurs in both normal and deficient rats, but it is far greater in extent and lasts a much longer time in deficient animals—two to three weeks in deficient animals, as against four to five days in normal ones. The vitamin A levels of the serum also rise and fall parallel with the lipids.

The similarity of the lipid response in deficient animals to the rise in serum lipids during convalescence from pneumonia in older children and in infants receiving vitamin A is striking. At the present time it cannot be claimed that this reaction is diagnostic of deficiency but only that it occurs in deficient animals.

The reason for the excessive rise in lipids and vitamin A of the serum after pneumonia is as obscure as the reason for the fall in vitamin A and lipids during pneumonia. It is evident that ingestion of vitamin A is usually necessary for the excessive rise in lipids to take place in patients under 2 years of age. The difference between the results in children over 2 years of age and in those under 2 years may, therefore, rest in the difference in the available vitamin A. It has been pointed out by numerous observers that infants have much lower stores of the vitamin than older children.[13] One should therefore expect to find that previous diet had an influence on the rise in lipids in convalescence. This was not found to be the case. Evidently there is much to be learned before it will be possible to explain the results. Two factors which may be mentioned are: (1) the sensitivity of the lipid reaction, which, as has been seen, is greatly increased in rats by the presence of vitamin A deficiency and which may be influenced also in other ways; (2) the presence of vitamin A in a physiologically active form. Vitamin A in storage is apparently physiologically inert[14]; it must be mobilized to be physiologically active, and the difference between the levels of older and of younger children may rest in the ease with which mobilization occurs. If such is the case, then the effect of the ingestion of vitamin A is to supply the vitamin in physiologically active form.

The rise in serum lipids in the rats after administration of vitamin A was looked on as an immediate physiologic effect of the sudden introduction of excessive amounts of vitamin A and the eventual return to normal as evidence of the adjustment of the body's processes to the continued presence of the excessive vitamin. The effect of deficiency was to injure in some way the body's "defense" so that the vitamin A acted with less opposition and the adjustment required a longer time to become effective. There is no objection to the application of the same reasoning to the rise in lipids after pneumonia, except that in the case of the rats it is known that deficiency was present, whereas in the case of patients with pneumonia it is known only that an infection was present and that the serum vitamin A was reduced but not absent.

Steiner and Turner,[3e] in commenting on the rise in cholesterol during convalescence from pneumonia, drew attention to a phenomenon that they had observed[15]; namely, that when thyroid is given to normal subjects for a time and then withdrawn the serum cholesterol rises from the low figures characteristic of hyperthyroidism to a point somewhat above the subject's normal level before

13. Wolff, L. K.: Schweiz. med. Wchnschr. **66**:979, 1936. Debré, R., and Busson, A.: Compt. rend. Soc. de biol. **114**:1162, 1933. Ellison, J. B., and Moore, T.: Biochem. J. **31**: 165, 1937. Woo, T. T., and Chu, F. T: Chinese J. Physiol. **15**:83, 1940.

14. Davies, A. W., and Moore, T.: Biochem. J. **28**:288, 1934.

15. Turner, K. B., and Steiner, A.: J. Clin. Investigation **18**:45, 1939.

returning to normal. The implied suggestion, that this occurrence may have a bearing on the course of the cholesterol content during and after pneumonia, is of extreme interest in the light of the suggestion of vitamin A–thyroid antagonism that arises from work done in Germany during the past decade.[16] Wendt[17] suggested that the adjustment of the organism to excessive administration of vitamin A might involve a compensatory increase in thyroid activity, though no evidence was given to support such a hypothesis.

The connection between the two suggestions may be summarized as follows: In the one case thyroid activity was increased until symptoms developed and then was suddenly withdrawn; in the case of the deficient rats, the thyroid "antagonist" (vitamin A) was withdrawn until symptoms developed and then was suddenly increased. The effect on the serum lipids was the same.[18]

There were 2 patients in this series in whom deficiency may be presumed to have been present (chart 14). In both the previous diet was extremely bad, in one leading to rickets and possibly scurvy, in the other leading to severe malnutrition. In neither were there any characteristics of vitamin A deficiency except the extreme reduction of serum vitamin A levels. In both the pneumonia was of significance rather because of the nutritional condition of the child than because of its intrinsic severity. In the first case (O. F.), no treatment was used except an adequate diet, sodium citrate being used for the rickets and ascorbic acid for the scurvy. In the second case (M. A.), carotene in oil was used for five days, but considering the lack of any effect from carotene in the other cases, it is doubtful whether the result could be attributed to the use of carotene. The results may be seen in chart 14. In both cases the rise in lipids was marked, and in that of O. F., who was receiving no supplement, the rise in vitamin A and eventually in the carotene was rather surprising. In the case of M. A. the rise in lipids was against the trend observed in other cases in which the patients were receiving equivalent doses of carotene.

The occurrence of this reaction in 2 cases in which deficiency was presumably present appears to be significant. However, in view of the apparent necessity for the ingestion of vitamin A to bring about the characteristic rise in lipids in the group under 2 years of age, the fact that the rise occurred spontaneously is puzzling. One may consider the rise in lipids in the deficient rats as an example of the general truth that a deficient organism is more sensitive to the substance in which it is deficient. It is difficult, however, to accept sensitivity as pronounced as would have to be present in these cases without further examples in which the diagnosis is less open to criticism. There is one example to be found in the literature. Steininger, Roberts and Brenner[19] in their study of experimental vitamin A deficiency in human beings gave vitamin A in relatively small dosage (1,000 units) to their subjects after they had been on the deficient diet for several months. The level of the vitamin rose to a point above that present before the start of the experiment before returning to the "normal" value. They were at a loss to explain

16. Clausen, S. W.: Pharmacology and Therapeutics of Vitamin A, J. A. M. A. **111**:144 (July 9) 1938.

17. Wendt, H.: Deutsche med. Wchnschr. **62**:1213, 1936.

18. It is not necessary to assume from this that thyroid activity is increased in pneumonia or that vitamin A is deficient; the indication is only that infection produces conditions that simulate those of hyperthyroidism or those of vitamin A deficiency as far as lipid metabolism is concerned. The mechanism by which infection does this is a problem for the future.

19. Steininger, G.; Roberts, L. J., and Brenner, S.: Vitamin A in Blood of Normal Adults, J. A. M. A. **113**:2381 (Dec. 30) 1939.

this occurrence, but it is possibly an example of extreme sensitivity acquired by a deficient organism.

If these are examples of the effect of deficiency, one must conclude that human beings become far more sensitive than rats or, to put it differently, the ability of human beings to adjust their metabolism to an increase in the physiologic activity of vitamin A is far more impaired by deficiency than that of rats, so much so that they may become sensitive merely to dietary improvement.[20]

SUMMARY

The vitamin A, carotene and total lipid of the serum are reduced in pneumonia. The reduction of these three elements, however, followed no regularity except that the longer the duration, the fewer the values that approached normal. Of the three, the vitamin A was the most rapidly reduced. The previous diet had a demonstrable influence on the carotene but not on vitamin A.

During convalescence the lipids of the serum of children over 2 years of age tended to rise to a point well above the normal and to remain there for a considerable time; the curve of serum vitamin A in general paralleled that of the lipids, but the peaks in individual cases did not necessarily coincide. In children under 2 years there was little tendency for the lipids to rise above the normal unless vitamin A supplement was given, when the rise in lipids approached more nearly that of the children over 2 years of age. In infants under 8 months of age there was little or no tendency for this abnormal rise of lipid level to occur.

While carotene levels could be correlated with lipid levels, correlation between the levels of vitamin A and of total lipid was absent during pneumonia and was low during convalescence. However, the similarity in the behavior of vitamin A and lipid levels leads to the conclusion that there must be a relationship—probably that both are subject to the same influences but that the speed and intensity of the reaction differ.

There appeared to be a definite correlation between lipid levels and the post-absorptive rise of vitamin A (vitamin A "tolerance" curve). It was also found that the rise in carotene four to five days after the ingestion of a carotene supplement was begun was related to the average lipid level during this period.

The abnormal rise in lipids in older children and in younger children receiving vitamin A during convalescence from pneumonia has been compared with a similar lipid reaction in deficient rats given excessive doses of vitamin A. The reaction is discussed as a possible aid to the diagnosis of deficiency, but it is felt that it should not be used for this purpose until more is known concerning the factors influencing it. The reaction is also discussed as a possible result of the physiologic activity of vitamin A.

20. That an organism adjusted to deficiency may at times become sensitive to a too abrupt administration of the deficient substances is indicated by two examples furnished by personal communication. Dr. Scroggie recently stated that in Chile, where a large portion of the population live on miserable diets, it is necessary to introduce the vitamins slowly and with a period of preparation, in which for a time a diet high in protein is given but no vitamins. Any attempt to introduce vitamins too quickly is followed by death. Mr. Owen Lattimore stated that horses used in the caravans crossing the mountains from Turkestan into India live for a considerable time on a scanty diet from which green fodder is lacking. If on arrival in India they are allowed at first to graze too freely, many of them may die.

TREATMENT OF GONORRHEAL VULVOVAGINITIS WITH SILVER PICRATE SUPPOSITORIES

REPORT OF RESULTS IN FIFTY-SEVEN CASES

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In the treatment of gonorrheal vulvovaginitis there are three general lines of attack: (1) application of a local antiseptic; (2) administration of an endocrine substance and (3) chemotherapy with a sulfonamide compound. The present study was begun in an effort to determine whether the first, which has often been thought to be obsolete, would not be as effective as either of the others if continuous medication could be employed. For this purpose silver picrate, which has been used successfully in the past in the treatment of gonorrheal vaginitis [1] and urethritis [2] as well as vaginitis due to Trichomonas vaginalis,[3] was chosen as the antiseptic. Infant size vaginal suppositories of silver picrate [4] were used for all patients treated in the clinic during the period of study. Results for all these patients are included in this report with the exception of those who transferred or lapsed before they had had sufficient treatment and observation to make any evaluation of the treatment possible. In many of these the condition was of long standing and chronic, the average duration of infection before treatment with silver picrate was begun being thirty-eight and seven-tenths weeks.

PLAN OF TREATMENT

In all cases treatment consisted of daily insertion of 1 silver picrate suppository for six days. Then there was one day without treatment, and a smear was taken before use of the suppositories was resumed. This was continued until the patient became free of symptoms and until there had been at least six weeks' treatment after the last positive smear. Then the patient was placed on observation, with weekly smears for the first three months and smears once a month for the second three months. No patient was discharged until after at least six months' observation. If symptoms recurred or the smear became positive, the silver picrate treatment was resumed. The average duration of the initial treatment was ten and four-tenths weeks. Thirty-two patients suffered relapses and were given a second course of silver picrate suppositories for an average of nine and eight-tenths weeks. Fifteen of this group showed one or more additional relapses. In 5 the vulvovaginitis was complicated on admission by urethritis and in 3 by proctitis. For these patients treatment consisted of local applications of 5 per cent mild protein silver.

From the Clinic of the Illinois Social Hygiene League, Chicago, Ill.

1. Kobak, A. J., and Frankenthal, L. E., Jr.: The Treatment of Cervicovaginitis in Children with Silver Picrate Suppositories, Am. J. Obst. & Gynec. **34**:292-298 (Aug.) 1937. Holmes, J. W.; Jones, J. A., and Gildersleeve, N.: The Treatment of Gonorrheal Vulvovaginitis in Children with Silver Picrate Suppositories, J. Pediat. **15**:86-90 (July) 1939.

2. Knight, F., and Shelanski, H. A.: Treatment of Acute Anterior Urethritis with Silver Picrate, Am. J. Syph., Gonor. & Ven. Dis. **23**:201-206 (March) 1939.

3. Corbit, J. D.; McElroy, R., and Clark, J. H.: Use of Silver Picrate in the Treatment of Vaginitis: A Five Year Study, J. A. M. A. **117**:1764-1766 (Nov. 22) 1941.

4. Furnished by John Wyeth & Brother, Inc.

RESULTS OF TREATMENT

Fourteen patients were discharged as cured after only one course of silver picrate. Ten more were apparently cured, but they lapsed before the full period of observation was completed. Twelve were discharged as cured after the second course of silver picrate treatment, and 2 more were apparently cured. After additional courses of treatment, 2 more were discharged and 1 was apparently cured.

In 10 cases the treatment resulted in failure, and in 6 the patient was not under treatment and observation long enough after a relapse to permit drawing of any definite conclusions.

Thus, in 41, or 72 per cent of the cases, the condition responded to this treatment, in 24 promptly and in 17 more slowly. In 10, or 17.5 per cent, the result was failure and in 6, or 10.5 per cent, the results were inconclusive.

COMMENT

No complications were observed during treatment. There was neither argyria nor any other reaction to the drug. The slender conical suppositories were inserted painlessly, some of the mothers even making a practice of inserting them while the patients were asleep. After the first few days most of the mothers were able to carry on the treatment at home and the patients were brought to the clinic once a week for smears. At the time this study was made, it was impossible for us to obtain satisfactory cultures for gonococci; hence no culture studies are reported.

CONCLUSIONS

A report on 57 unselected patients with gonorrheal vulvovaginitis treated with silver picrate vaginal suppositories is presented. There were included many chronic as well as acute infections. In 42 per cent of the cases the condition responded promptly and in 30 per cent more slowly. In 17.5 per cent the treatment resulted in failure, and in 10.5 per cent the results were inconclusvie.

At present I believe this type of treatment to be second only to the use of sulfathiazole and to be the treatment of choice for patients who do not tolerate that drug or are refractory to it.

STUDIES IN IMMUNITY TO PERTUSSIS

II. EFFECT OF STIMULATING DOSE OF HAEMOPHILUS PERTUSSIS VACCINE

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KATHARINE M. HOWELL, M.D.
CHICAGO

CAPTAIN EDWARD J. DENENHOLZ
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
MARTHA JANOTA, M.S.
AND
ROBERTA STANARD, R.N.
CHICAGO

In a previous communication [1] we reported our observations made after vaccination of prematurely born children with phase I Haemophilus pertussis vaccine, both by clinical means and by the opsonocytophagic test. We observed that a characteristic immunity curve (as measured by the opsonocytophagic test) was obtained from injection of phase I H. pertussis vaccine, viz., that a peak was reached two months after the last injection and that in most instances the curve gradually declined to a base line level three years after inoculation. Similar observations were previously reported by Kendrick, Gibbs and Sprick.[2]

Since the immune titer had dropped to a low level, the effect of a stimulating dose of 2 cc. of phase I H. pertussis vaccine (10,000,000,000 per cubic centimeter) given two years after the initial vaccination with 8 cc. of phase I H. pertussis vaccine was studied. The basis for this study was a group of 42 prematurely born children ranging in age from 2½ to 8 years, 41 of whom we were able to follow over an extended period.

Opsonocytophagic tests (the measure of immunity) were made at the time the stimulating dose was given and were repeated two to four months later and again two and one-half to three years later. The method and technic of the test were those which have been carefully described by Kendrick and her co-workers.[2] Before receiving the stimulating dose of 2 cc. of phase I H. pertussis vaccine, 65.8 per cent of these 41 children had weak or negative immune titers as measured by the opsonocytophagic test and 34.2 per cent had medium or strong titers.

Two to four months after reimmunization, 90.2 per cent of the 41 children had strong or medium titers, while only 9.8 per cent had titers in the negative or weak groups. The blood of 15 children indicated that the opsonocytophagic ratings which were obtained two to four months after reimmunization were the same as those obtained at the time the stimulating dose was administered. Eleven, or 73.3 per cent, of these 15 had medium opsonocytophagic ratings; 3 had weak ratings

Aided by grants from The Upjohn Company and from the Michael Reese Research Foundation.

From the Sarah Morris Hospital for Children and the Department of Bacteriology, Nelson Morris Institute for Medical Research, Michael Reese Hospital.

1. Rambar, A.; Howell, K.; Denenholz, E.; Goldman, M., and Stanard, R.: Studies in Immunity to Pertussis, J. A. M. A. **117**:79-85 (July 12) 1941.

2. Kendrick, P.; Gibbs, J., and Sprick, M.: The Opsonocytophagic Test in the Study of Pertussis, J. Infect. Dis. **60**:302-311 (May-June) 1937.

and 1 a negative rating. Thus the immune titers of the 73.3 per cent of the children who showed no increase already were in the moderate group. This would appear to indicate that maximum immunity may have been obtained by the children whose titers were in this group and that further stimulation was impossible. The 1 child with a negative rating contracted whooping cough. This coincides with the findings as previously reported that infants who subsequently contract whooping cough demonstrate a low opsonocytophagic rating before the onset of the disease. Four months after the onset of the disease in this child the opsonocytophagic titer had increased from a negative to a medium rating.

For 25 children within two to four months after the stimulating dose had been given the opsonocytophagic rating increased in the following manner: One increased from negative to strong; 2, from negative to medium; 9, from weak to strong; 11, from weak to medium, and 2, from medium to strong. The immune titer of 1 child decreased from a strong to a medium rating.

Twenty-six of the group of 41 children under observation were retested two and one-half to three years after the stimulating dose had been given. At the time the stimulating dose was given 69.2 per cent of these 26 children had immune titers in the negative or weak group and 30.8 per cent in the medium or strong

Opsonocytophagic Ratings of 41 Children Before and After Stimulating Dose of Phase I H. Pertussis Vaccine

	Strong	Medium	Weak	Negative
At time of reimmunization	1	13	23	4
Two to three months after reimmunization	12	25	3	1
Comparison of Opsonocytophagic Ratings of 26 of the 41 Children Before and After Stimulating Dose of Phase I H. Pertussis Vaccine				
At time of reimmunization	0	8	14	4
Two to three months after reimmunization	8	14	3	1
Two and a half to three years after reimmunization	3	19	3	1

group. After the restimulating dose of phase I H. pertussis vaccine, the titers at the end of two and one-half months and at the end of two and one-half years were as follows: The blood of 85 per cent of these 26 children indicated immune titers of strong and medium ratings and of 15 per cent negative and weak. A comparison of the immune titers at the time of the stimulating dose and two and one-half to three years later indicated that 17 of the 26 children, or 65 per cent, still had higher opsonocytophagic ratings at the end of two and one-half to three years than at the time of the reimmunization. The increase in these instances was as follows: Eleven increased from weak to medium rating; 3, from negative to medium; 1, from weak to strong; 1, from negative to strong, and 1, from medium to strong. Six children had the same immune titers, of which 5 were in the medium and 1 in the weak group. Three children had lower ratings than at the time of reimmunization, 1 decreasing from the weak to the negative group and 2 decreasing from the medium to the weak group.

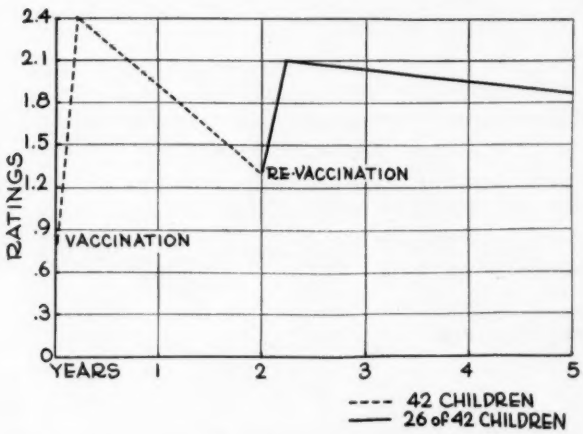
The opsonocytophagic rating of the 26 children two and one-half to three years after reimmunization, as compared with the ratings of these same children two to four months after reimmunization, are summarized as follows: Nine children had lower opsonocytophagic ratings, of which 5 decreased from strong to medium, 2 from strong to weak, 1 from medium to weak and 1 from medium to negative.

Eleven children had the same rating, 10 being in the medium and 1 in the strong group.

Six children had higher opsonocytophagic ratings, of which 2 increased from medium to strong, 3 from weak to medium and 1 from negative to medium. The child whose immune titer increased from negative to medium had contracted whooping cough one year and four months after the stimulating dose had been given, and the increase in titer was undoubtedly due to active immunization after contraction of the disease. In the other 5 cases, the peak of immunity may not have been reached at the time of the two to three month tests or, if it had been reached, natural acquired immunity may have played a role in further increasing the titers. The summary of the opsonocytophagic ratings and a composite curve following vaccination and revaccination are presented in the table and the chart.

CONCLUSIONS

This study appears to indicate that a stimulating dose of phase I H. pertussis vaccine injected two years after an initial pertussis vaccination causes immunity to



Graphic presentation of opsonocytophagic ratings. A rating of 3 + is given to the strong group, 201 or more; 2 + to the medium group, 101 to 200; 1 + to the weak group, 26 to 100, and 0 to the weak group, 0 to 25.

whooping cough as measured by the opsonocytophagic test as the immune titer rose in those children in whom it had dropped to a low level. This rise is for the most part maintained two and a half to three years after the stimulating dose. In instances in which the immunity was already present at the time of the stimulating dose (2 cc. of phase I H. pertussis vaccine), no further response was elicited on reinoculation, and most of the immune titers remained high for two and one-half to three years after the stimulating dose. For example, the curve of the opsonocytophagic ratings fell only from 2.12 to 1.93 during the two and one-half to three year observation period. Since the opsonocytophagic test is apparently a reliable index of immunity, it, rather than an arbitrary time limit, should be used whenever possible as a guide to revaccination. This study shows that for most children yearly restimulation with H. pertussis vaccine is not indicated and is not necessary once the two year revaccination has been given, because the opsonocytophagic index has remained high during the three years of study. Observations on the immunity of this group of children will be continued.

CARDIAC MUSCLE IN POLIOMYELITIS

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After the publication of the recent paper of Saphir and Wile entitled "Myocarditis in Poliomyelitis" [1] we were stimulated to review our autopsy records of poliomyelitis with particular reference to the histologic changes in the heart. These authors reported a series of 7 cases, in 6 of which myocarditis of varying degree was found on microscopic study. As pointed out by them, the literature contains no reference to myocarditis in poliomyelitis. The usual changes in the cardiac muscle in poliomyelitis are toxic or degenerative, as described by Landon and Smith.[2] These changes include a varying degree of right-sided dilatation and a tendency toward flabbiness in the consistency of the musculature, pallor and at times even notable friability. On microscopic examination, there may be interstitial edema, congestion, capillary hemorrhage at times and granular degeneration of the cytoplasm of the muscle, rarely to the point of loss of striations, however. At times slight fatty and hydropic changes are noted in muscle cells.

From September 1938 to and including January 1941, 9 cases of poliomyelitis have come to autopsy at the Philadelphia Hospital for Contagious Diseases, 1 in 1938, 2 in 1939, 5 in 1940 and 1 in 1941.

The ages of the patients in this series ranged from 2 years to 30 years. Two were adults, and the remainder were children. All were white; 7 were males and 2 were females. All presented fairly typical clinical and postmortem conditions, although an occasional unusual occurrence was noted, which will be mentioned in the brief reports of the cases which follow.

REPORT OF CASES

CASE 1.—A. M., a white boy 12 years of age, entered the hospital with the chief complaints of sore throat, fever, nausea, vomiting, malaise, weakness of the left side of the face, difficulty in swallowing, weakness of both upper extremities and intercostal paralysis. On the day after admission the respirations became irregular and the pulse rate fell to 60 per minute. He died nine days after the onset of the illness. Autopsy confirmed the clinical diagnosis of acute anterior poliomyelitis of the bulbospinal type. In addition, there was early bronchopneumonia. No myocarditis was seen on histologic study of the cardiac muscle.

CASE 2.—J. K., a white boy 14 years old, was admitted to the hospital on the fourth day of illness and died on the fifteenth day. There was weakness of the left shoulder and difficulty in swallowing. The respirator was required because of rapid shallow respirations. Autopsy disclosed acute anterior poliomyelitis of the bulbospinal type and hypostatic pneumonia.

Microscopically, there were found minimal myocardial inflammatory changes, characterized by congestion, swelling of the endothelial cells lining some of the vessels and sparse accumulations of cells around blood vessels in the interstitial tissues. These were chiefly mononuclear in nature, although occasional polymorphonuclear leukocytes were seen. In addition, a few foci of lymphocytes were found beneath the epicardial fat.

CASE 3.—C. H., a 14 year old white boy, entered the hospital on the third day of illness and died on the fifth day. There were weakness of all extremities and a relative bradycardia associated with ectopic beats. Treatment in the respirator was instituted on the day before

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1. Saphir, O., and Wile, S. A.: Myocarditis in Poliomyelitis, Am. J. M. Sc. **203**:781, 1942.
2. Landon, J. F., and Smith, L. W.: Poliomyelitis: A Handbook for Physicians and Medical Students, New York, The Macmillan Company, 1934.

death. Autopsy confirmed the clinical diagnosis of acute anterior poliomyelitis of the bulbospinal type. In addition there was pulmonary edema. There was no microscopic evidence of myocarditis.

CASE 4.—W. Q., a 2 year old white boy, entered the hospital with the chief complaints of paralysis of both upper extremities, cyanosis and respiratory distress. He was immediately placed in the respirator, but only slight improvement resulted. The duration of illness was three days.

The gross changes noted at autopsy were typically those of acute poliomyelitis. Microscopic study, however, revealed intense eosinophilic infiltration throughout all of the tissues, which we

Fig. 1 (case 6).—Microscopic section, showing the inflammatory reaction involving the vessel and surrounding tissue and simulating necrotizing arteritis.

felt might represent the lesions of eosinophilic leukemia, although we have no antemortem blood studies to support this conclusion. The patient died within eleven hours of admission to the hospital, before laboratory studies could be instituted, and unfortunately no bone marrow was obtained at autopsy, because the clinical picture appeared to be fairly typical. Parasitic infection and periarteritis nodosa were considered as possibilities, although no parasites were identified grossly or microscopically and there was no evidence of necrotizing arteritis. Tissues from the lungs were prepared with Goodpasture's stain and gram-positive cocci resembling streptococci were visualized. The heart showed intense interstitial and perivascular inflammatory cellular infiltration, the majority of the cells being of the eosinophilic series. The exact nature of this eosinophilic response remains in doubt, although eosinophilic leukemia

seems a likely possibility. Perhaps it represents the response on an allergic basis to streptococci, although many of the eosinophils appear to be of the young type.

CASE 5.—H. H., a 10 year old white girl, was admitted to the hospital approximately five days after onset of an illness characterized by malaise, slight fever, abdominal pain, nausea and impairment of speech. It is interesting to note that she had been in another hospital for treatment of active rheumatic pancarditis and while there she was exposed to a patient who had acute anterior poliomyelitis. Physical examination revealed difficulty in swallowing and weakness of all extremities, although she was able to make muscular movements. There

Fig. 2 (case 7).—Microscopic section, showing minimal perivascular response. Similar changes were shown on sections in case 2.

were prolongation and roughening of the mitral first sound and a rough systolic apical murmur. On the day of death she complained of cardiac pain and restlessness. The duration of illness was six days. At autopsy, the heart was slightly enlarged, the result of right-sided dilatation. The epicardial surface was lusterless. The mitral valve leaflets were thickened by edema, and they were covered at their line of contact by a thin row of firm, yellow, fibrinoid, bead-like vegetations, typical of the lesions of rheumatic endocarditis. The posterior intimal lining of the left atrium was thickened and wrinkled. The cause of death was acute anterior (bulbospinal) poliomyelitis complicating acute rheumatic pancarditis.

Microscopic examination of the heart presented the typical histologic findings of acute rheumatic pancarditis, including the presence of characteristic Aschoff bodies.

CASE 6.—N. R., a white boy 12 years of age, died on the fifth day of illness. He had shallow respirations, difficulty in swallowing and weakness of the right side of the face. After one day in the respirator his pulse became imperceptible. At autopsy there was gastric dilatation. The cardiac aspect of the stomach was injected and presented severe shallow ulcerations surrounded by red areolas of mucosal tissue. Numerous petechial and macular hemorrhages were scattered throughout the mucosal surface. The gastric contents were a dark brown sour-smelling fluid resembling acidified blood. The bronchial tree contained similar-appearing fluid, and the pulmonary fields showed patchy bronchopneumonia. The heart on microscopic study presented an inflammatory reaction in the nature of a necrotizing

Fig. 3 (case 8).—Section of myocardium, showing definite acute interstitial myocarditis.

arteritis and arteriolitis with inflammatory cellular infiltration throughout the wall of the vessel and extending outward to cause perivascular and interstitial accumulations.

CASE 7.—W. Q., an 11 year old white boy, died after a duration of illness of thirty days. There was intercostal paralysis necessitating use of the respirator. Postmortem examination disclosed moderate right-sided dilatation of the heart and extensive atelectasis and bronchopneumonia of the left lung. The right lung showed compensatory emphysema. Minimal myocarditis similar to that described in case 2 was found on histologic examination.

CASE 8.—C. B., a white man 25 years of age, had a duration of poliomyelitis of sixty-four days. About thirty days after the onset of illness, his pulse rate suddenly rose to 150 per minute and the volume was poor. Cyanosis and weak, thready pulse characterized his terminal

physical signs. Autopsy disclosed right-sided dilatation of the heart, flabbiness of the cardiac muscle, early pulmonary suppuration in the lower lobe of the left lung and a small, well localized, focal abscess in the middle lobe of the right lung.

Microscopic study of the heart disclosed definite myocarditis with congestion, interstitial edema and perivascular cellular infiltration, including scattered polymorphonuclear leukocytes. This was somewhat more extensive than that noted in cases 2 and 7 but still scarcely to be described as more than minimal.

CASE 9.—H. M., a 30 year old white woman, was placed in a respirator immediately on admission to the hospital. The duration of the disease was six days. Autopsy disclosed mild dilatation of the right ventricle. There was no bronchopneumonia.

Microscopic examination revealed a minimal myocarditis similar to that described in case 2.

COMMENT

Gross examination of the heart in all 9 cases revealed no noteworthy pathologic changes other than some loss of the normal color and consistency. Microscopically, however, the sections of the heart in all of the cases revealed degenerative changes of varying degree, including some loss of striations, fragmentation of muscle bundles, granular degeneration, interstitial edema and swelling and pyknosis of nuclei. In some of the cases patchy areas of myosclerosis were visualized. In addition, evidence of a demonstrable myocarditis of some degree was noted in 7 of the 9 cases. Two of these, i. e. cases 4 and 5, presented complicating pathologic features which caused the deletion from the series. Of the 7 cases suitable for analysis, in 2 (cases 1 and 3) there were no inflammatory changes. In the other 5 cases, however, there was an actual histologic myocarditis of variable but minimal degree. These changes were characterized as being vascular, perivascular and interstitial in their distribution with actual cellular infiltration of the tissues. It is interesting to speculate whether or not the virus of poliomyelitis may be the agent directly responsible for these inflammatory changes or whether it is a virus plus an associated or secondary organism, perhaps of the nature of a streptococcus. Rosenow [3] has contended that a pleomorphic streptococcus bears an etiologic relationship to poliomyelitis. Unfortunately, blood cultures were not made for these patients; these might have been of help in arriving at a definite conclusion had the results been positive. From the clinical standpoint and from the gross and microscopic studies of the heart in these 5 cases rheumatic fever can be eliminated as the cause of the myocarditis. It is perhaps pertinent to note that in all the cases the poliomyelitis was of the bulbospinal type and that the period of its clinical manifestation varied from three to sixty-four days.

In the accompanying table we have enumerated several factors which we thought might be contributory etiologic factors. Age and sex apparently play no part in the picture, although we have not sufficient patients in all age groups to allow us to make this statement without some measure of hesitation. The duration of the disease seems to bear no relationship to the severity of the cardiac lesion. Consideration of the year in which the disease was contracted shows that in all of the cases of the 1940 series there was some degree of myocarditis, and yet in 1 case in 1939 and 1 in 1941 there were similar changes; hence we feel that this factor plays no part in the pathologic process, although it may be possible that the virus of one season or the virus in association with another organism differs in its effects on the heart from that of another season. The presence of bronchopneumonia was considered, but in case 7 there was the most extensive bronchopneumonic consolidation with only minimal changes in the myocardium, while in case 1 with early bronchopneumonia there was no myocarditis and in case 9 with minimal myocarditis

3. Rosenow, E. C.: Streptococci in the Lesions of Experimental Poliomyelitis in Monkeys, Proc. Soc. Exper. Biol. & Med. **27**:444, 1930.

there was no evidence of consolidation. Bronchopneumonia associated with myocarditis does occur, but this is not a common or usual complication, as was pointed out by Stone.[4] Clinical symptoms of rapid, thready pulse and cyanosis would appear from our experience to be suggestive of myocarditis, as in cases 6 and 8, with the more characteristic pathologic changes, these symptoms were present, although prior to postmortem examination myocarditis was not suspected. Anticipating the objection that similar myocardial changes might be seen in the other acute diseases of childhood, we rechecked the records of the microscopic examination of the heart in our autopsies from February 1941 to the present, which included cases of all the acute exanthems except smallpox and German measles and of pertussis, and in none of these except the cases of acute fulminating scarlet fever was interstitial myocarditis reported.

SUMMARY AND CONCLUSIONS

In 7 of 9 cases of poliomyelitis myocarditis of some degree in addition to toxic and degenerative changes was shown on histologic examination of the cardiac

Summary of Clinical and Pathologic Findings

Case	Year	Age, Yr.	Sex	Duration of Disease, Days	Symptoms Referable to Cardiovascular System	Degree of Myocarditis	Pathologic State of Lungs	Complicating Diseases
1	1938	12	M	9	Pulse rate of 60 per minute	None	Early broncho-pneumonia	None
2	1939	14	M	15	None	Minimal (+)	Hypostatic pneumonia	None
3	1939	14	M	5	Bradycardia and ectopic beats	None	Edema	None
4	1940	2	M	3	None	Moderate (+++)	None	Eosinophilic infiltration
5	1940	10	F	6	Cardiac pain	Moderate (+++)	None	Acute rheumatic pancarditis
6	1940	12	M	5	Imperceptible pulse	Moderate (++)	Bronchopneumonia	None
7	1940	11	M	30	None	Minimal (+)	Bronchopneumonia	None
8	1940	25	M	64	Rapid thready pulse of poor volume; cyanosis	Minimal (++)	Pulmonary suppuration	None
9	1941	30	F	6	None	Minimal (+)	None	None

muscle. In 1 case the poliomyelitis was complicated by acute rheumatic pancarditis and in another by a possible eosinophilic leukemia, and these cases are therefore deleted from the series. We have attempted to correlate the year of the disease, sex, age, duration of symptoms and presence of pulmonary pathologic conditions with the presence or absence and the degree of myocarditis, but we feel that these factors play no part in its production. The clinical signs of cyanosis and rapid, thready pulse are suggestive of myocarditis in poliomyelitis, although none of our patients died in myocardial failure and in no instance was myocarditis suspected clinically. This relatively high incidence of myocarditis (71 per cent—in 5 of 7 uncomplicated cases) in fatal poliomyelitis suggests the possibility of a virus or a virus plus a secondary organism, perhaps of the nature of a streptococcus as the cause. We should advise electrocardiographic studies and blood cultures in all cases of poliomyelitis in an attempt to correlate these findings.

3401 North Broad Street.
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4. Stone, W. J.: Heart Muscle Changes in Pneumonia: Remarks on Digitalis Therapy, Am. J. M. Sc. **163**:659, 1922.

ERYSIPELAS IN INFANCY

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Erysipelas is a red, spreading, indurated demarcated lesion involving the lymphatics of the skin and caused by streptococci immunologically and culturally members of the Lancefield group A but of no serologic type. In an infant, although the temperature may be elevated to 106 F., convulsions seldom occur (in 2 of our series of 42 patients). The indurated lesion may begin within a few hours after the onset of the fever with the appearance of cellulitis, but clearly demarcated edges rapidly develop. In a newborn infant it may begin in the umbilical region, in a lesion from forceps abrasions or from impetigo neonatorum, or commonly in the diaper region. Later in infancy it more commonly begins from an otitis media, acute rhinopharyngitis or impetigo. The lesion may spread more rapidly in infants than in older patients and seems to undergo rapid exacerbations at times until the administration of sulfanilamide is started, and even then this occasionally happens.

Erysipelas, like other streptococcic diseases, has responded well to sulfanilamide therapy. Many cases have been reported illustrating the beneficial effects of this sulfonamide compound, but most of the patients were in the older age group. Since the mortality is highest in infancy and beyond 55 years, we have made a study of the patients with erysipelas admitted to Louisville General Hospital and Children's Free Hospital in Louisville. The patients from 1932 to 1936 comprise the first group, and those from 1937 to the present, who have been treated with sulfanilamide, the second group. The infants treated with sulfanilamide generally received 1½ grains per pound (0.2 Gm. per kilogram) of body weight per day until the temperature was normal for several days. This treatment has varied, of course, through the years, because of different residents' being on the service.

As early as 1936 Meyer-Heine and Huguenin [1] reported 8 cases of erysipelas in infants below 1 year of age, of whom all were treated with sulfamidochrysoidine hydrochloride (a compound supposedly identical with the original prontosil [4-sulfamido-2,4-diaminoazobenzene hydrochloride]) and all recovered. In 1937 the *Journal of Pediatrics* published a symposium on sulfanilamide therapy. In the articles of this symposium 27 cases were reported in which children below 3 years of age were treated with sulfanilamide. Of the 27 children there were 5 less than 1 month of age, 2 of whom lived. All of the 23 children from 1 month to 3 years lived. In our series of 18 the 2 below 1 month of age died, while all of the 16 from 1 month to 3 years old lived. Before sulfanilamide was used, Brennemann [2] cited a mortality rate of 76 per cent for children below 1 month of age and 46 per cent for children up to 2 years of age.

Usually with sulfanilamide treatment there is a rapid fall of the temperature, over an average period of twenty-seven hours in our cases, except in 1 case, in

From the Department of Pediatrics, University of Louisville School of Medicine.

1. Meyer-Heine, A., and Huguenin, P.: Presse méd. **44**:454, 1936.

2. Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1941.

Data on Eighteen Patients Treated with Sulfanilamide

Case	Name	Sex	Race	Age, Mo.	History and Physical Condition	Dosage of Sulfanilamide *	Temperature Normal in Hours	Transfusions	Comment	Hospital Days Due to Erysipelas
1	C. E. R.	M	N	½	4 day duration; convulsion; thighs, penis and scrotum involved; some lesions in axilla, on eyelids and on elbow; condition critical on admission	0.6 Gm. on admission; 0.3 Gm. every 3 hr. (8)	..	0	Gangrenous scrotum; death	1
2	J. P.	M	W	28	3 in. band on left ankle, also on left knee and on right ankle	0.6 Gm. on admission; 0.3 Gm. every 4 hr. until discharge	24	0	Cleared rapidly	5
3	D. H.	M	W	19	Began from impetigo; 4 in. band around left leg on admission	1 Gm. on admission; 0.3 Gm. every 4 hr.	30	0	Cleared rapidly	5
4	J. B.	M	W	18	Entire buttock and perineum; puncture wound in center	0.6 Gm. every 2 hr. (3); 0.3 Gm. every 4 hr. (6); 0.3 Gm. 4 times a day	116	0	Cleared rapidly	10
5	B. H.	F	W	10	2 day duration; right leg involved	1 Gm. every 2 hr. (3); 0.6 Gm. every 6 hr. (8); equal amount of sodium bicarbonate	24	0	Cleared rapidly	6
6	G. B.	F	N	10	Impetigo 10 days before admission; erysipelas 3 days before; whole side of leg involved; otitis media on left side	0.6 Gm. every 2 hr. (2); 0.3 Gm. every 4 hr. (4 days); 0.3 Gm. 3 times a day (1 day) equal amount of sodium bicarbonate	48	0	Cleared rapidly	8
7	J. A. W.	M	N	7	Fever and convulsions; entire leg below knee involved; femoral glands enlarged	0.3 Gm. every 4 hr (4) for 3 days; 1 dose of 0.6 Gm. after first dose	4	0	Drug started after 24 hr.; temperature normal in 4 hr.	6
8	G. R. B.	F	W	28	Onset 7 days before admission; upper part of left leg and lower ¾ left thigh involved	0.6 Gm. every hr. (2); 0.3 Gm. every 4 hr. (6 days); equal amount of sodium bicarbonate	48	0	Cleared rapidly	6
9	J. T.	F	N	20	Impetigo 1 week; vomiting, fever and irritability; entire right leg involved	0.3 Gm. every 4 hr. (5 days); equal amount of sodium bicarbonate	24	0	Cleared rapidly; magnesium sulfate packs	5

10	Baby B.	M	N	New born	Discharging left eye on 6th day; lesion spread to left lip, cheek and side of nose	0.15 Gm. every 2 hr. (4) for 8 days; no drug 2 days; 0.15 Gm. every 2 hr. (4); equal amount of sodium bicarbonate	..	3	Multiple abscesses; Bact. dysenteriae Flexner; died	15
11	L. L. H.	F	W	24	Developed from week old sore on right leg; lower third of leg involved; infected burn on hand	0.6 Gm. every 2 hr. (3); 0.3 Gm. every 4 hr.; equal amount of sodium bicarbonate	30	0	Cleared rapidly	6
12	D. M. H.	F	W	6	Onset 3 days before admission; forehead involved	1 Gm. on admission; 0.3 Gm. every 4 hr. (15); equal amount of sodium bicarbonate	8	0	Cleared rapidly	5
13	M. E. M.	F	W	7	5 day old burn; 7 × 9 cm. lesion on right leg; 1 child in family died with erysipelas	0.6 Gm. on admission; 0.3 Gm. every 4 hr. (4 days); equal amount of sodium bicarbonate	12	0	Cleared rapidly	7
14	R. W.	M	W	15	Suppurative otitis media; entire left leg and foot involved; 1 dose of drug in another hospital	0.3 Gm. every 3 hr. (2 days); 0.3 Gm. every 4 hr. (3 days); 0.3 Gm. 4 times a day (3 days); equal amount of sodium bicarbonate	28	2	Cleared rapidly	8
15	W. L. S.	M	W	10	Impetigo 10 days before admission; lesions spread 1 day before; erysipelas in multiple places; entire left hip and ⅔ of left leg involved	0.6 Gm. every 2 hr. (2); 0.3 Gm. every 4 hr. (3 days); 0.15 Gm. every 4 hr. (7 days)	30	0	Cleared rapidly, but patient remained in hospital until 13th day because of impetigo	7
16	A. S.	F	W	8	Red place on leg lanced (no pus); lanced 2 weeks later (no pus); rapid spread over thigh and buttocks; abscess in left ischiorectal fossa; labia involved	1 Gm. on admission; 0.5 Gm. every 6 hr. (4 days); 0.3 Gm. every 6 hr. (3 days); equal amount of sodium bicarbonate	12	4	Stay in hospital and fever due to abscess; transfusions later; drug used later for abscess; total stay in hospital 67 days	6
17	S. A. C.	F	W	14	Scratched 3 days before admission: area lateral side of right leg; mother ill with severe streptococcic infection	0.6 Gm. on admission and 4 times a day (5 days); then 4 times a day (3 days); equal amount of sodium bicarbonate	16	0	Cleared rapidly; saline solution packs	8
18	W. G. W.	M	W	2	Suppurative otitis media 2 days before admission; 6 × 6 cm. lesion on left cheek (same side as infected ear)	0.6 Gm. on admission; 0.3 Gm. every 4 hr. (2); 0.15 Gm. every 4 hr. (4 days); 3 days later 0.15 Gm. every 4 hr. (2 days)	48	3	Stay in hospital prolonged by anemia and draining ears to 13 days	8

* Figures in parentheses indicate number of doses administered or number of days the indicated dosage was continued.

which it remained elevated until the fifth day. In our 24 cases occurring before the introduction of sulfanilamide the duration of fever averaged six and six-tenths days, although this series included 2 cases in which the patient died in less than two days after admission to the hospital.

Only 4 of 18 patients who were given sulfanilamide received transfusions, and 1 of these received the blood after the erysipelas had cleared; the transfusion was given as treatment of an abscess which the patient had before the erysipelas developed. However, 19 of 24 patients not treated with the drug received transfusions, an average of three per child.

The average number of days in the hospital due to the erysipelas of the patients treated with sulfanilamide was six and six tenths, while before the introduction of sulfanilamide the average was twelve days each.

The only complication in our group of 16 patients who lived was a secondary anemia in 1 case, which cleared with transfusion. However, we had a child with a gangrenous scrotum and one with multiple abscesses and dysentery. Both were newborn, and both died. The complications mentioned in the "Symposium on Sulfanilamide" were: cyanosis, 8 cases[3]; recurrence of the erysipelas, 1[4]; abscesses, 5[5]; acidosis, 1[3b]; jaundice, 1 (the patient died),[3b] and generalized peritonitis and gangrene, 1 (the patient died).[6]

REPORT OF CASES

Both of our patients who died were newborn.

CASE 1.—Erysipelas developed in the lower part of the back and on the legs of a 13 day old Negro boy. This was treated with "salve" at home for four days. The child then had a convulsion and was brought to the hospital in a critical condition. He had erysipelas involving both thighs and the back, penis and scrotum, and smaller areas over one eyelid, in the right axilla and on the left elbow. The scrotum rapidly became gangrenous. He received 0.6 Gm. of sulfanilamide on admission and 0.3 Gm. every three hours for ten doses, at which time he died. The treatment was augmented with magnesium sulfate packs and sedation, but the child died thirty-two hours after admission.

CASE 2.—The patient was a Negro boy born in the hospital. The onset of the erysipelas occurred on the sixth day from a discharging left eye. This spread rapidly to the left cheek and the nose and then on down to the left shoulder and arm. An abscess developed in the left shoulder on the third day despite the administration of 0.15 Gm. sulfanilamide every two hours for four doses a day; this dosage was continued for eight days. The patient received an amount of sodium bicarbonate equal to that of sulfanilamide. The use of sulfanilamide was then discontinued for two days, after which its use was resumed for two days, until death. A retrobulbar abscess had developed behind the infected eye. An abscess developed in the occipital region, and hemolytic staphylococci (Staphylococcus aureus) were obtained on culture. Diarrhea developed, and two cultures revealed Bacterium dysenteriae (Flexner). A roentgenogram of the skull showed a cloudy nasal sinus on the left side. He received three transfusions of 50 cc. each but died fifteen days after onset of the erysipelas, at 21 days of age.

CONCLUSIONS

If the few cases presented may be considered as any criterion, the following assumptions may be drawn:

1. The mortality rate for infants below 1 month of age has not been relatively affected by the use of sulfanilamide, whereas the mortality rate for infants above this age is approaching zero.

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3. (*a*) McIntosh, R.; Wilcox, D. A., and Wright, F. H.: J. Pediat. **11**:167, 1937. (*b*) Carey, B. W.: ibid. **11**:202, 1937. (*c*) Basman, J., and Perley, A. M.: ibid. **11**:212, 1937.
4. Mitchell, A. G., and Trachsler, W. H.: J. Pediat. **11**:183, 1937.
5. Hageman, P. O.: J. Pediat. **11**:195, 1937. Basman and Perley.[3c]
6. McQuarrie, I.: J. Pediat. **11**:188, 1937.

2. The fall of temperature is much more sudden.
3. Steady improvement takes place early.
4. The use of erysipelas antitoxin and ultraviolet rays is not necessary.
5. Fewer transfusions are necessary.
6. Magnesium sulfate packs need to be used only for localizing abscesses.
7. Complications are still relatively frequent.
8. The stay in the hospital is reduced 50 per cent.
9. The best dosage of sulfanilamide seems to be 1½ grains per pound (0.2 Gm. per kilogram) of body weight per day divided into six or eight equal doses, the first dose being twice the amount of the following doses. This should be continued for three to four days after the temperature is normal, to prevent a recurrence.

NUTRITION AS A CONDITIONING FACTOR IN THE RHEUMATIC STATE

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Many environmental influences associated with unhygienic living have been considered important in the development of rheumatic fever. Whether such living conditions may condition the host to rheumatic fever is unknown; however, it has been shown [1] that these factors increase susceptibility to infections of the respiratory tract, predispose to complications and promote the spread of hemolytic streptococci. The evidence available to date indicates that overcrowding exerts its effect through the factor of infection. But, in addition, there is some factor associated with being underprivileged which increases susceptibility of the host to rheumatic fever. To determine whether this conditioning factor may be a faulty dietary, we have conducted nutritional surveys in the city of New York and tested the effect of a reenforced diet on rheumatic children at the Pelham Home. The present paper includes data from these studies.

PROCEDURE

This study is based on the diet records of three groups of children, 100 in all, obtained between October 1939 and June 1941. Each record covers a period of one week and is believed to be representative of the dietary of the individual child.

Description of the Three Groups.—It seemed desirable for control purposes to have one group of children in whom rheumatic fever did not occur. For this purpose students in a private day school for girls seemed well suited. The school selected had an annual matriculation of over 500 children and for at least six years had been free of rheumatic fever. All of the children were under the care of a pediatrician. In 2 sisters, following pneumonia during a summer's vacation, a systolic apical murmur developed. With this possible exception the entire student body had been free of physical signs of rheumatic heart disease for at least six years. The group of subjects from this private school consisted of 50 girls in good health. None of them had a history or physical signs of rheumatic disease. All of them were white, between the ages of 5 and 12 years, natives of the city of New York and living in the highest economic stratum, yet they were attending a girls' school situated on the East River in an environment where rheumatic fever is common. Each child recorded a diet for one or two weeks during the winter and spring months. These records were used for analyzing the dietary data of nonrheumatic children.

It seemed advisable to select for the rheumatic group city school children and adolescents who had been under the care of a physician for at least five years. We therefore chose a group of young ambulatory rheumatic subjects on whom continuous clinical and bacteriologic observations had been made for five years or longer. Erythrocyte sedimentation rates and antistreptolysin titers were determined after every infection of the respiratory tract caused by hemolytic streptococci. Patients in whom rheumatic activity developed were admitted to either the Babies Hospital or the Presbyterian Hospital. The city school group consisted of 100 children, all of whom had one or more attacks of rheumatic fever with cardiac involvement. So far as could be determined, none of them had active disease during the periods when their dietary records were made. These children included boys and girls, white and Negro, attending

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1. Coburn, A. F., and Pauli, R. H.: J. Exper. Med. **56**:609, 1932.

various city schools of New York. In addition to being rheumatic subjects they were all of the lower economic stratum. Each child recorded his diet for one week during three different seasons. Since little seasonal difference was noted, the fifty most complete records from the 50 patients with whom the longest clinical contact had been made were selected for analysis.

These rheumatic children from the city schools were subdivided into two groups of 25 each on the basis of their susceptibility over a period of several years. Twenty-five patients who had had several rheumatic attacks with a recrudescence in the preceding two years were included in the more susceptible group. The other 25, who had escaped rheumatic fever from two to ten years, were placed in the less susceptible group. Both groups were exposed to and contracted hemolytic streptococcic infections; both groups came from similar tenements and from families comparable in size, race and intelligence. Whether or not there was a difference in income or a difference in the amount spent on food was not determined.

Instructions to Patient and Parent.—Each family cooperating in this study was visited at mealtime by a trained field worker, the graduate nurse in charge of our rheumatic disease clinic, who outlined our objective, to obtain a week's record of all food ingested by the rheumatic subjects. The families were requested not to alter their diets in any way. Subsequent visits were made during meal hours, and when cooperation seemed satisfactory a printed booklet was left to be filled in after each meal by the patient. This form, with simple instructions for recording the kinds and amounts of food taken, was prepared by the nutritionist collaborating in this investigation.

Information Obtained from Records.—The data collected refer to food ingested. No deductions were made for waste; the data on consumption refer to quantities actually eaten. The nutritive value of the meals was estimated by applying average figures on composition to the data on food ingested. The calculations on food composition were taken from published complications.[2] Whatever errors occur in these data, due to losses from cooking processes, storage and aging, should be randomized throughout. The nutritive value of the diets was computed in terms of calories and proteins; minerals (calcium, phosphorus and iron), and vitamins (vitamin A, thiamine, riboflavin, ascorbic acid and vitamin D). Calculations of nicotinic acid amide and other food factors the distribution of which is not yet known were of necessity omitted.

Adequacy of Diets.—The one hundred diets were analyzed in the following ways:

1. According to the classification of Stiebeling and Phipard [3] the intake of each constituent was classified as good, fair or poor.

2. An estimation was made of the adequacy or inadequacy of vitamin foods as suggested by Munsell.[4]

3. The percentage of excess or deficiency in the various components was computed. In determining excess or deficiency, the food ingested was compared with the requirements for the age and sex of the child as proposed by the National Research Council.[5] All computations represent the average intake of food for the week plus vitamin preparations taken to reenforce the diets.

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2. Chatfield, C., and Adams, G.: Proximate Composition of American Food Materials, Circular 549, United States Department of Agriculture, 1940. Bowes, A. D., and Church, C. F.: Food Values of Portions Commonly Used, ed. 2, Philadelphia, The Authors, 1939.

3. Stiebeling, H. K., and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities, Circular 507, United States Department of Agriculture, 1939.

4. Munsell, H. E.: J. Am. Dietet. A. **17**:311, 1941.

5. Recommended Daily Allowances for Specific Nutrients, Medical Preparedness, J. A. M. A. **116**:2601 (June 7) 1941.

4. In order to assess statistically the influence of the several dietary factors in the two groups of rheumatic subjects, the data were studied without being related to any accepted standard. For each dietary constituent the individual amounts ingested by the 50 children were arranged in rank order of magnitude so that the children could be divided into two groups: those who ingested less than the median amount and those who ingested more than this amount. The distribution of more susceptible and less susceptible children in each of the two categories was then counted. This method of analysis leads to a 2×2 contingency table[6] from which a value for chi-square can be computed. In such a table a value for

TABLE 1.—*Protein in Diet and Recurrent Activity in Rheumatic Fever*

Protein in Diet	More Susceptible Subjects	Less Susceptible Subjects	Total
Below medium	18	7	25
Above medium	7	18	25
Total	25	25	50

TABLE 2.—*Distribution of Dietary Constituents Estimated According to Stiebling*

		Private School	Less Susceptible Rheumatic Subjects	More Susceptible Rheumatic Subjects
Protein	Good	44	20	8
	Fair	6	5	16
	Poor	0	0	1
Calcium	Good	48	23	19
	Fair	2	2	6
	Poor	0	0	0
Phosphorus	Good	37	19	9
	Fair	13	5	13
	Poor	0	1	3
Iron	Good	50	25	25
	Fair	0	0	0
	Poor	0	0	0
Vitamin A	Good	43	19	7
	Fair	7	6	13
	Poor	0	0	5
Thiamine	Good	20	4	4
	Fair	29	21	17
	Poor	0	0	4
Riboflavin	Good	26	9	3
	Fair	24	16	18
	Poor	0	0	4
Ascorbic acid	Good	48	20	14
	Fair	2	3	7
	Poor	0	2	4

chi-square in excess of 6.6 indicates the existence of a significant association ($P <$ 1 per cent) between rheumatic susceptibility and the quantity of the dietary component ingested.

A single illustration of the method is presented in table 1. The marginal totals in this table indicate that the 50 children included 25 who took a lower amount of protein and 25 who took a greater amount; they also indicate that 25 of the children were from the more susceptible group and 25 from the less susceptible group. Of the 25 who ingested the lower amount of protein there were 18 with the higher degree of rheumatic susceptibility and 7 with the lower degree. In contrast, of the 25 children who ingested the higher amount of protein, a minority, namely 7, were in the more susceptible category and the majority, 18, were in the less

6. Fisher, R. A.: Statistical Methods in Research Workers, ed. 7, London, Oliver & Boyd, 1938.

susceptible group. The value of chi-square of 9.7 indicates a significant association between the level of protein in the diet and rheumatic susceptibility.

SUSCEPTIBILITY TO RHEUMATIC FEVER IN RELATION TO NUTRITIVE VALUE OF THE DIET

Classification of the quantity of each dietary constituent as good, fair or poor showed that the private school girls had the best diets, the less susceptible rheumatic group diets not quite so good and the more susceptible rheumatic group the poorest diets. The three groups are compared in table 2.

The private school girls satisfied Munsell's requirements except for cereals and bread. Of 50 girls 28 ingested less than the required amount of these foods.

TABLE 3.—*Distribution of Deficiencies in Consumption of Important Foods*

		Individual Diets Showing Deficiency in Indicated Component						
	Subjects	Eggs	Milk	Butter	Green Vegetables	Cooked Vegetables	Meat and Fish	Cereal and Bread
Private school	50	0	0	0	0	0	2	28
Less susceptible rheumatic subjects	25	3	2	6	1	0	10	12
More susceptible rheumatic subjects	25	13	9	10	9	6	14	13

TABLE 4.—*Food Consumption of the Three Groups Compared with National Research Council Requirements*

	Fifty Private School Girls					Twenty-Five Less Susceptible Rheumatic Subjects					Twenty-Five More Susceptible Rheumatic Subjects				
	Number Receiving			Percentage Deviation from Requisite		Number Receiving			Percentage Deviation from Requisite		Number Receiving			Percentage Deviation from Requisite	
	Excess	Requisite	Deficiency	Average	Median	Excess	Requisite	Deficiency	Average	Median	Excess	Requisite	Deficiency	Average	Median
Protein	45	1	4	+24	+21	7	10	8	+ 5	0	2	5	18	—13	—17
Calories	20	8	22	+ 2	0	1	2	22	—19	—15	1	1	23	—27	—28
Calcium	33	1	16	+12	+10	10	4	11	+ 1	0	2	4	19	—19	—17
Phosphorus	48	0	2	+35	+33	15	4	6	+ 9	+ 7	4	7	14	— 9	— 7
Iron	39	1	10	+37	+38	4	4	17	— 9	— 9	2	5	18	—18	—20
Vitamin A	46	2	2	+170	+118	11	2	12	+ 9	— 5	1	0	24	—44	—50
Thiamine	30	9	11	+22	+10	4	8	13	—22	—27	0	6	19	—29	—36
Riboflavin	42	0	8	+39	+33	20	1	4	+43	+35	14	4	7	+10	+ 8
Ascorbic acid	46	3	1	+90	+70	16	3	6	+29	+15	6	9	10	— 4	—10
Vitamin D	21	3	26	+25	0	6	1	18	—39	—90	2	0	23	—82	—93

Fifteen, 8 and 12 children failed to eat the optimum of eggs, milk and butter respectively; however, no two of these deficiencies occurred in the same child, and they were compensated for by reenforcement with vitamins A and D in 25.

The 25 less susceptible rheumatic children were similar to the private school girls in consuming adequate amounts of vegetables, meat and fish and in their deficiency of cereals and bread. In the consumption of eggs and butter 3 patients showed a deficiency that was not compensated for by other food or by reenforcement with fat-soluble vitamins.

The 25 more susceptible rheumatic subjects were similar to the subjects in the two previous groups in consumption of cereals and bread. Deficiency in green and cooked vegetables appeared in the diets of 9 and 6 subjects. Fifteen consumed inadequate quantities of eggs, 10 of milk and 11 of butter, and only 4 reenforced their diets with vitamins. These findings are summarized in table 3.

Data on the ingestion of the various food components in relation to the National Research Council requirements are presented in table 4.

This table shows that the diets of the private school (nonrheumatic) girls were adequate in calories and contained most of the other components in excess. In contrast, the diets of the city school (rheumatic) children were deficient in many components; however, riboflavin and ascorbic acid seemed to be adequate. Both the more susceptible and the less susceptible subjects showed a comparatively low intake of calories, iron, thiamine and vitamin D. The averages showed that the diets of the less susceptible subjects were adequate in protein, calcium, phosphorus and vitamin A, whereas the diets of the more susceptible subjects were deficient in these four components.

NUTRITIVE VALUE OF THE DIETS IN THE TWO RHEUMATIC GROUPS

Calories.—Most of the diets of both the more susceptible and the less susceptible subjects were moderately low in calories. The median deviation from requisite for the 50 patients was — 24 per cent. Of the half showing a greater deficiency, 16 were in the more susceptible group and 9 in the less susceptible group. The association between caloric intake and susceptibility to rheumatic recrudescences was not statistically significant, chi-square being only 2.

Protein.—The difference in dietary deficiency between the two groups was striking. Seventy-two per cent of the diets of the more susceptible patients were low in protein, as compared with 32 per cent of those of the less susceptible group. The median deviation from requisite for the 50 patients was 0 per cent. Of the half showing a deficient intake, 18 were in the more susceptible group and 7 in the less susceptible group. With this distribution chi-square equals 9.7. This indicates that the association between greater susceptibility and a deficient intake of protein is statistically significant.

Calcium.—The distribution of calcium deficiency in the two groups was similar to that of protein, 76 per cent in the more susceptible and 44 per cent in the less susceptible group. The median deviation from requisite of 50 patients was — 15 per cent. Seventeen of the 25 that showed a deficiency greater than — 15 per cent were in the more susceptible group. With this distribution chi-square equals 6.5, almost a statistically significant association between calcium deficiency and greater susceptibility.

Phosphorus.—The medians of both the more susceptible and the less susceptible subjects were normal. A few more patients were deficient in the more susceptible group than in the less susceptible. The association between deficiency and greater susceptibility was not statistically significant.

Iron.—Of the more susceptible subjects 72 per cent and of the less susceptible 68 per cent were deficient in iron ingested. The median deviation from requisite for both groups was — 16 per cent. Eighteen of the 25 patients showing a deficiency greater than this were in the more susceptible group. As in the case of protein, chi-square equals 9.7.

Vitamin A.—Of the five vitamins computed the ingestion of vitamin A only showed a striking difference in the diets of the two groups. Ninety-six per cent of the more susceptible and only 48 per cent of the less susceptible patients were deficient in vitamin A intake. The median deviation from requisite for 50 patients was — 30 per cent. Eighteen of the 25 patients showing a greater deficiency were in the more susceptible group. As in the case of protein, there was a statistically significant association between susceptibility to rheumatic fever and vitamin A deficiency, with chi-square equaling 9.7. A breakdown into U. S. P. units of the vitamin obtained from the animal and plant sources showed the median values for the less susceptible subjects to be 4,840 from animal sources and

4,900 from vegetable sources. For the more susceptible subjects the corresponding values were 2,280 and 2,340. In the high income, private school group the values were 10,580 and 4,960.

Thiamine, Riboflavin, Ascorbic Acid and Vitamin D.—The distribution of deficiency and excess in the diets of the more susceptible and of the less susceptible patients were similar. For none of these four vitamins did there appear to be an association between susceptibility to rheumatic fever and deficiency. All of these data are combined in table 5.

An examination of the relationships found between rheumatic susceptibility and the series of dietary factors analyzed in this study indicates highly significant associations between susceptibility and several of the components, namely, protein, iron and vitamin A. Moreover, the associations with calcium and riboflavin are measured by chi-square values of 6.5; that is, they have almost attained the 1 per cent level of significance. Although other factors in the analysis did not yield

TABLE 5.—*Distribution of Essential Dietary Components Among the Two Rheumatic Groups*

	Percentage of Patients Deficient		Contingency Table Distributions			
Dietary Component	More Susceptible	Less Susceptible		More Susceptible	Less Susceptible	Chi-Square
Calories	92	88	Below median	16	9	2
			Above median	9	16	
Protein	72	32	Below median	18	7	9.7
			Above median	7	18	
Calcium	76	44	Below median	17	8	6.5
			Above median	8	17	
Phosphorus	56	24	Below median	16	9	2
			Above median	9	16	
Iron	72	68	Below median	18	7	9.7
			Above median	7	18	
Vitamin A	96	48	Below median	18	7	9.7
			Above median	7	18	
Thiamine	76	52	Below median	14	11	2
			Above median	11	14	
Riboflavin	28	16	Below median	17	8	6.5
			Above median	8	17	
Ascorbic acid	40	24	Below median	16	9	2
			Above median	9	16	
Vitamin D	92	72	Below median	15	10	2
			Above median	10	15	

significant chi-square values in every instance, the association with susceptibility is in the positive direction. This result suggests strongly that many of the relationships may be determined, not by the component itself, but by the deficiencies with which it was associated in the diets actually ingested by the children. It is well known that diets low in one dietary essential are apt to be low in several. Reference to the table indicates no deficiency in either of the groups in phosphorus, ascorbic acid or riboflavin. Moreover both groups were approximately equally deficient in vitamin D. It is clear that such associations as were found between these factors and rheumatic susceptibility must have resulted because these deficiencies happened to be associated with other more important factors. It is therefore not possible to ascribe a specific role of etiologic importance to any one of the dietary factors, although the association of better diets and worse diets in general with susceptibility is apparent.

It may, however, be inquired whether or not combined deficiencies of several dietary essentials are more significant than single deficiencies. In table 6 the data for each of the two groups have been distributed so as to indicate the possible combinations among deficiencies in protein, vitamin A, iron and calcium. These

four dietary factors were selected not because it is justifiable to assign to them greater importance than to some of the other factors but rather because in our analysis these factors yielded the highest chi-square values and because the dietary records indicated deficiencies of them in an appreciable number of the records. The table is important in showing a large number of less susceptible children who received adequate intakes of all of these elements, as contrasted with a large number of more susceptible children who were deficient in all of them.

It is not possible to carry the statistical analysis to an evaluation of the significance of multiple deficiency in all of these four factors, since the number of subjects deficient in all items is small. However, it is possible to study the association between combined deficiency in two essentials and susceptibility to rheumatic fever. Thus there were 32 children of the 50 whose intakes of both protein and vitamin A were either above or below the median intake for the group. The distribution of these children with respect to rheumatic susceptibility is illustrated in table 7. The value of chi-square from this table of 12.5 is higher than was

TABLE 6.—*Distribution of Combined Deficiencies in the Two Groups of Rheumatic Patients*

	Protein −								Protein +							
	Vitamin A −				Vitamin A +				Vitamin A −				Vitamin A +			
	Ca −		Ca +		Ca −		Ca +		Ca −		Ca +		Ca −		Ca +	
	Fe −	Fe +	Fe −	Fe +	Fe −	Fe +	Fe −	Fe +	Fe −	Fe +	Fe −	Fe +	Fe −	Fe +	Fe −	Fe +
Less susceptible....	0	0	1	1	4	0	0	1	0	1	0	4	2	1	1	9
More susceptible....	11	0	1	2	3	0	0	1	0	2	1	1	0	1	2	0

TABLE 7.—*The Distribution of Combined Deficiencies of Protein and Vitamin A in Relation to Rheumatic Susceptibility*

Vitamin A and Protein in Diet	Less Susceptible Subjects	More Susceptible Subjects	Total
Above median in both constituents	13	3	16
Below median in both constituents	2	14	16
Total	15	17	32

Chi-square (after Yates's correction) = 12.5; P = 0.0005.

obtained with any single dietary element, in spite of the fact that the total number of children used in the anaylsis was appreciably lower. Similar analyses for combined deficiencies of protein and calcium (36 children) and for combined deficiencies of calcium and vitamin A (28 children) yielded values for chi-square of 11.1 and 11.8 respectively. These findings lead one to believe that several deficiencies may be more important in influencing susceptibility than any one dietary factor.

Two clinical records will serve to illustrate some of these differences in diet and susceptibility between the more susceptible and the less susceptible patients.

PATIENT REM. (less susceptible group).—This 14 year old boy has been under our observation for twelve years. He is of Italian extraction, the son of an office worker, one of three brothers living in a small but clean apartment. His father had had rheumatic fever, and both brothers had had mild attacks when they were about 6 years old. The patient was born prematurely during the seventh month, and a severe attack of rheumatic fever with carditis developed after his first hemolytic streptococcic infection, at the age of 22 months. Although he contracted a number of hemolytic streptococcic infections of the respiratory tract during childhood, he escaped clinical symptoms and laboratory signs of rheumatic activity. His presystolic murmur disappeared and his heart returned to normal size.

Comment.—Because of the familial history, the early onset of rheumatic fever and the exposure to the respiratory pathogens of his environment, it was felt in 1930 that the outlook for his future was ominous. However, his susceptibility to rheumatic fever seemed to disappear and he developed into a normal healthy adolescent.

PATIENT D'AM. (more susceptible group).—This 19 year old youth has been under our observation for fifteen years. He is of Italian parentage, the son of a piano mender, one of five children, living in an overcrowded and poorly kept apartment. His father's family had had a history of rheumatic fever; in one sister a mild rheumatic attack developed during this study. The patient had severe rheumatic fever with carditis at the age of 4 years. After another severe attack, at the age of 7, his tonsils were removed. During the succeeding decade he had numerous streptococcic infections, each of which was followed by a severe attack of rheumatic fever. With the exception of a period of sulfanilamide prophylaxis he had one rheumatic attack each year, necessitating eight admissions to a hospital. Cardiac damage was progressive, with aortic and mitral valvular lesions becoming severe.

Comment.—Both of these rheumatic families included several children living in small apartments and contracting periodically the streptococcic infections prevalent in the city of New York. The former had a higher income and fewer mouths to feed, was more intelligent and enjoyed a much better dietary, as is seen in table 8.

TABLE 8.—*Differences in Diet Between a Less Susceptible and a More Susceptible Subject*

	Patient Rem. (Less Susceptible Group)			Patient D'Am. (More Suspectible Group)		
	Daily Intake	Percentage of Excess	Percentage Deficient	Daily Intake	Percentage of Excess	Percentage Deficient
Protein	104	63	..	51	.....	50
Fat	129	..	..	66	.....	..
Carbohydrate	383	..	..	151	.....	..
Calories	3,023	20	..	1,822	.....	52
Calcium	1,693	42	..	0.570	.....	65
Phosphorus	2.101	62	..	0.883	.....	35
Iron	17.18	42	..	9.46	.....	40
Vitamin A	15,875-16,236	98-62	..	3,967-4,350	.....	50-56
Thiamine	563-623	40-4	..	311-379	.....	35-52
Riboflavin	2.4	142	..	0.7	.....	27
Ascorbic acid	97-127	54-27	..	25-32	.....	50-68
Vitamin D	16-110	.....	94-86	10-70	.....	96-91

In 7 of the rheumatic subjects included in this investigation severe rheumatic attacks developed shortly after their diets were analyzed. Five of these had been classified as more susceptible and 2 as less susceptible subjects. All were living on poor diets at the time that they contracted streptococcic pharyngitis. The deficiencies both in nutritive value and in the actual foods consumed are shown in table 9.

The use of poor diets by the more susceptible patients was due probably to economic reasons in most instances. However, another reason for inadequacies in their diets was the aversions of these children to certain types of foods. Twenty-one of 25 children had strong dislikes for more than one important food constituent. The number of children showing intense aversions for green vegetables was 13; for eggs, 7; for liver, 7; for fish, 7, and for meat, 5. No attempt was made to force them to eat the foods disliked.

FEEDING PROBLEMS AMONG RHEUMATIC CHILDREN OF WEALTHY FAMILIES

The rarity of rheumatic fever among children receiving the advantages of life in the higher economic stratum is well recognized. Occasionally, however, a wealthy child enjoying the privileges of the best hygienic environment contracts rheumatic fever following streptococcic pharyngitis. We have collected data on

a small group of rheumatic children whose family budgets could supply the best diets to determine whether there was anything unusual in their dietary histories.

The 14 patients comprising this group were children seen in consultation, referred by their family physicians. Most of them were seen only once. Their mothers were questioned concerning their early history, habits, tastes and diets from infancy. Specific questions asked included whether the child presented a feeding problem, whether there was a difference between the rheumatic child and other members of the family in taste for foods, whether any particular foods had been omitted from the diet or whether the child ate everything prior to the onset of rheumatism. The answers to these questions are summarized in table 10.

TABLE 9.—*Dietary Analyses of 7 Patients in Whom Rheumatic Attacks Developed During This Study*

Patient	Calories	Protein	Calcium	Phosphorus	Iron	Vitamin A	Thiamine	Riboflavin	Ascorbic Acid	Vitamin D	Eggs	Milk	Butter	Green Vegetables	Cooked Vegetables	Meat or Fish	Cereal and Bread
Ho.....	D*	A*	D	A	A	D	D	A	A	D	A	A	D	A	A	A	A
Ma.....	D	D	D	D	D	A	D	D	A	D	D	D	A	A	A	A	D
Mi.....	D	A	D	A	A	A	D	A	A	A	D	D	A	A	A	A	A
As.....	D	A	A	A	A	D	A	A	A	D	D	A	A	A	A	A	A
Wa.....	D	D	D	A	D	D	A	A	D	D	A	A	A	D	D	D	A
Gr.....	D	D	D	D	D	D	D	A	A	D	A	D	D	A	A	D	D
Ch.....	D	D	D	D	D	D	D	A	D	D	D	D	A	D	D	D	D
Number adequate.....	0	3	6	3	3	2	2	5	6	1	3	3	5	5	5	4	4
Number deficient.....	7	4	1	4	4	5	5	2	1	6	4	4	2	2	2	3	3
Total.....	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7

* D = deficient; A = adequate or less than 10 per cent deficient.

TABLE 10.—*Dietary Abnormalities Among Rheumatic Children of Highest Economic Level*

Patient	Age	Sex	Dietary History
C. A.	6	F	No eggs or butter; believed sensitive to eggs
E. H.	4	F	Difficult feeding problem; poor appetite since the age of 10 months; given vitamin B and cod liver oil
H. R.	5	F	Cyclic vomiting since infancy; eats any food
I. S.	10	M	Unable to eat cream, cheese or white of egg
I. D.	13	M	Normal
K. C.	8	F	Always refused eggs and fresh vegetables
K. J.	12	M	Still declines eggs and green vegetables
K. D.	16	F	Food allergy; omitted eggs because of hives
L. A.	5	M	Difficult feeding problem; always refused eggs
P. E.	9	F	Because of pyelitis when 2 years old, omitted eggs and meat
S. L.	3	F	Feeding problem; always refused eggs
T. J.	4	M	Feeding problem; slow eater; would not eat vegetables
W. A.	9	M	Omitted eggs; possibly sensitive to them
V. R.	11	M	Always avoided eggs and chocolate; believed to be harmful to him

The histories of these 14 unselected rheumatic children show a high incidence of feeding problems in early childhood. Ten children did not eat eggs. Only 1, the son of a physician, had the normal menu of a wealthy family.

PRELIMINARY OBSERVATIONS ON THE USE OF A REENFORCED DIET AT PELHAM HOME

This study was made to determine whether rheumatic susceptibility might be modified by improving the nutrition of rheumatic children over a long period of time. For preliminary observations children with quiescent rheumatism at Pelham Home seemed satisfactory test subjects. Most of these patients had been under our observation for several years, and it was known that except when taking sulfanilamide prophylactically they had contracted streptococcic infections of the

throat which were followed by at least a 50 per cent incidence of rheumatic recrudescences. It was also known that the Home, with a budget of $1.46 per day per child, spent 30 cents daily for each child's food. The diets were approximately adequate in all constituents except vitamin D.

It was observed in the field studies previously described that one of the foods usually omitted by more susceptible rheumatic children, either because of its cost or the patient's taste, was eggs. For this reason and since eggs are rich in so many essential factors, they seemed well suited as a reenforcing agent for this study. The basal diet just adequate except for vitamin D and perhaps for vitamin C was reenforced each day with two eggs boiled five minutes and two frozen egg yolks. As soon as eggs were added to the basal diets the children complained that they "did not have eggs at home" or "never liked eggs"; however, after the first week there was no difficulty in having the eggs consumed.

None of the patients received any medicines or added vitamins. All were examined once a week by a physician and questioned for rheumatic symptoms daily by a nurse. Two cultures were obtained from the throat each week, and the sedimentation rate of the blood was determined twice each month. The rectal temperature and the pulse rate were recorded morning and night. Strains of hemolytic streptococci recovered from patients on admission were considered carrier

TABLE 11.—*Observation on Children at Pelham Home Receiving Egg-Reenforced Diet*

	1939-1940	1940-1941
Total patients on special diet	17	26
Number escaping hemolytic streptococcic infections	4	15
Number contracting hemolytic streptococcic infections	13	11
Serologic types of hemolytic streptococci recovered by throat culture	6, 13, 24, 28, 29	9, 11, 18, 27
Number of rheumatic attacks	0	0

strains. Only group A organisms which appeared for the first time in a patient's throat some weeks after arrival are recorded in this study. Each type reported appeared in at least 2 patients within a short period.

Results.—Three overweight children lost an average of 4 pounds (1.8 Kg.). The other children gained an average of 8 pounds (3.6 Kg.). Children with active rheumatism seemed unaffected by the addition of eggs to the diets. The children with quiescent rheumatism who contracted infections of the respiratory tract with hemolytic streptococci escaped clinically recognizable rheumatic fever, although they showed a rise in antistreptolysin titer and in some instances a slight elevation of the erythrocyte sedimentation rate. The group was small, and facilities were not available for making adequate control studies. Furthermore, rheumatic fever was not severe in the city of New York during this period of study. Therefore, final evaluation of these results awaits the accumulation of more observations with controls. The preliminary data are summarized in table 11.

It is of interest that after the reenforcement of the Pelham Home diets with four eggs a day the customary susceptibility to rheumatic fever was not apparent. This is in accord with observation of English investigators. Warner, Winterton and Clark [7] stated:

> But perhaps the most striking fact suggesting that an increase in the animal fat in the form of fresh milk and butter may be of prophylactic value is furnished by the figures from Christ's Hospital where the incidence of rheumatism was reduced to less than a third, corresponding to a rise in the animal fat consumption from 50.6 to 103.6 grm.—due largely to an increase in the rations of milk and butter.

7. Warner, E. C.; Winterton, F. G., and Clark, M. L.: Quart. J. Med. **4**:227, 1935.

Of children in St. Andrews, Reading and Cardiff they wrote:

> It does appear, however, that the consumption of animal protein and of dairy products by the rheumatic children and by the control children of this social status is low, and the intake of carbohydrate, particularly in the form of potatoes, is high.[8]

COMMENT

Three factors appear to be essential to the genesis of the rheumatic state. The first of these is a constitutional factor, transmitted by the genes as a mendelian recessive,[9] which modifies the metabolism of the host in some manner as yet unknown. So far as can be determined in a mixed metropolitan population about 5 per cent of human subjects are constitutionally susceptible to the development of rheumatic fever. Maturation of the rheumatic process in this 5 per cent depends, however, on at least two other concomitant factors. One of these, the factor of infection, is hemolytic streptococci, whose products precipitate the rheumatic attack. If hemolytic streptococci are inactive as respiratory pathogens, rheumatic fever does not occur, although the general population may contain 5 per cent of susceptible hosts. When infections of the respiratory tract with these organisms become prevalent, as in the city of New York during the late winter and spring months, rheumatic attacks follow. But these attacks are distributed differently from the preceding streptococcic infections. About 1 to 3 per cent of infected children in the lower economic strata contract rheumatism, whereas the wealthy, with rare exceptions, escape. When rheumatic fever occurs in the home of a wealthy family, it is usually among the domestics, in a young maid or cook; rarely does rheumatic fever occur in a child of the family, and in such an unusual instance a history suggesting dietary deficiencies can often be elicited.

The extraordinary inequality in distribution of rheumatic fever between the economic classes is a fact well recognized and widely investigated by students of rheumatic disease. It is well known that the disease has a higher incidence and is more severe in growing children than in mature adults. And there is general agreement that rheumatic fever is more common in the cities than in the country districts. British and Dutch observers have pointed out a striking difference in the severity of rheumatic disease between the children of the rural Netherlands and of industrial urban England. Among the children of the Netherlands [10] there were only 228 deaths from rheumatic heart disease in the five year period of 1920 to 1925, whereas in the industrial cities of England rheumatic fever was an important cause of death in childhood. Since there is no great difference in climate, race, age or incidence of infections of the respiratory tract affecting the children of these two countries, who show a striking difference in response to infection, one must consider the presence of a third essential factor in industrial urban populations and its lack in rural communities. This factor we believe may be the "conditioning of the host" by a poor diet. Paul indicated the importance of conditioning of the host in his valuable epidemiologic studies [11] when he concluded:

> An appreciation of this process tends to minimize the idea that the *clinical entity of rheumatic fever* may be precipitated in a normal individual as a result of his first contact with the infectious agent (presumably the hemolytic streptococcus). It tends to magnify the importance

8. From our point of view this control group who escaped rheumatic fever may have been by heredity not susceptible.

9. Wilson, M. G., and Schweitzer, M. D.: J. Clin. Investigation **16**:555, 1937.

10. Van Breemen, J., in Proceedings of the Conference on Rheumatic Diseases, Bath, Hot Mineral Bath Committee of The Bath City Council, 1928, chap. 7, p. 39.

11. Paul, J. R.: Rheumatic Fever in New Haven, New York, Milbank Memorial Fund, 1941.

of susceptibility in this disease as an evolved characteristic. One almost concludes that the infant *must grow up to be a rheumatic.*

The evolution of rheumatic susceptibility occurs principally among children who have lived on poor diets. Our data show an association between susceptibility and combined dietary deficits in protein, vitamin A, calcium and iron. It is not yet known whether the lack of one or more of these constituents plays a role in the rheumatic process. The importance of iron, not only for formation of hemoglobin but also as a component of cytochromic enzyme systems essential in intracellular oxidations, is well recognized. Iron requirements increase tremendously at puberty, but the incidence of rheumatic fever falls precipitously at this age. If iron deficiency were significant in the causation of rheumatic fever, the disease should become intense at puberty.

Of some interest is the possible significance of a low intake of calcium throughout childhood. Calcium plays an essential role in the normal irritability of nerve and muscle tissue, in the clotting of blood and perhaps in the permeability of membranes, all of which may be altered in rheumatic fever. The absorption of calcium from the gastrointestinal tract is dependent on ingestion of adequate amounts of vitamin D or on exposure of the body to sunlight, neither of which is sufficiently available to rheumatic children. Although severe rickets is not common in rheumatic children, the striking prevalence of poor musculature and dental development among these children may well reflect a mild prolonged deficiency of calcium.

That at least ten of the twenty-two amino acids known to be present in proteins are essential to and not synthesized by human beings is established. The functions of these amino acids in cellular metabolism are not known; however, it seems clear that proteins are essential components of all the known intracellular enzyme systems and play a fundamental role in the repair of tissues, especially of those organs with heavy work loads, such as the heart. Furthermore, proteins are the most costly of foods, especially those of great use in repairing tissues: eggs, meats and dairy products. That a lack of those proteins most useful in growth and repair may be important in conditioning a subject to rheumatism is compatible with all observations made during this study.

It is not known at present whether vitamin A has a function in the metabolism of mesodermal cells. Recent reports[12] indicate that reenforcement of the diet with vitamin A will not protect against rheumatic fever. Nevertheless, since this was the only vitamin for which there was a statistically significant association between susceptibility to rheumatic fever and dietary deficiency, we have investigated vitamin A metabolism in rheumatic subjects. These investigations showed a close relationship between poor diets and low levels of vitamin A in the blood plasma in patients in whom the disease is quiescent. The onset of rheumatic activity precipitated a further decline in the plasma level of the vitamin. A full report of these observations is the subject of a following paper.

SUMMARY

This study was undertaken to determine whether nutrition during childhood can be considered an important factor in the genesis of the rheumatic state. The observations indicate a close association between nutrition and rheumatic susceptibility. Highly susceptible subjects had poor diets. These diets were not, however, low in a single component but nearly always in so many factors that

12. Kuttner, A. G.: J. Clin. Investigation **19**:809, 1940. Warner, Winterton and Clark.[7]

evaluation of the relative importance of one essential was precluded. It is possible that a deficiency in a single element, such as a protein component, may be important in the genesis of rheumatic fever; however, to know whether reenforcement with an excess of any single factor will suffice to protect against rheumatic susceptibility, physicians must await the results of a direct test of rheumatic children living in large cities of the temperate zones.

CONCLUSIONS

These studies indicate that there is a relation between poor diets and susceptibility to rheumatic fever.

It appears that deficiencies in several factors may be more important than a deficiency in any one dietary factor in conditioning the subject to the rheumatic state.

Dr. Charles L. Hoagland, Dr. A. Ashley Weech and Miss Irene Waters gave advice in this study.

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SECOND ATTACKS OF ANTERIOR POLIOMYELITIS

REPORT OF FOUR CASES

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The incidence of second attacks of anterior poliomyelitis assumes considerable importance, both as a possible indication of the immunity which is developed from the disease and in differential considerations for patients who have previously had anterior poliomyelitis. Second attacks of this disease would seem to be extremely rare. Fischer and Stillerman,[1] in an analysis of all so-called second attacks of poliomyelitis reported prior to 1938, were able to collect 13 which they considered authentic, to which they added certain others. Although the number of cases reported is remarkably few, even a few cases may be significant considering the low incidence of poliomyelitis in the general population.

At the Harvard Infantile Paralysis Commission, while following 6,000 cases of poliomyelitis, we have encountered 4 in which the findings were such as to allow a diagnosis of a second attack of the disease. It is significant that all 4 of the patients in question were under observation before, up to and subsequent to the time of the second attack.

REPORT OF CASES

CASE 1.—*First Attack.*—R. O., a boy aged 4 years, became ill on Sept. 12, 1923 with headache, vomiting, drowsiness and a high fever. The next day it was noticed that his legs were sensitive and his neck was stiff. Paralysis developed, and his physician made a diagnosis of anterior poliomyelitis. The spinal fluid was not examined.

He was referred to the clinic of the Harvard Infantile Paralysis Commission on November 13, approximately two months after the original acute illness. The extremities were hypersensitive, particularly on straight leg raising, and examination of the muscles showed a patchy paralysis of flaccid type involving both legs, the abdomen and the back. The paralysis was extensive; eight muscles were rated functionally "poor," and fifteen were "fair," with many others involved to a lesser extent. The findings at that time were typical of anterior poliomyelitis. The patient was observed and treated regularly in the clinic. There was gradual return of muscular power, but a certain amount of residual paralysis remained. The last examination of his muscles was two weeks prior to his second attack.

Second Attack.—On Aug. 31, 1928, thirteen days after his sister was discharged from the hospital with the diagnosis of anterior poliomyelitis, this patient, now 8 years 11 months of age, was admitted to the Children's Hospital complaining of headache, vomiting, drowsiness and fever of two days' duration.

Physical examination at the time of admission revealed pronounced spasm on forward flexion of his head and stiffness of his back associated with a temperature of 101 F. The temperature dropped to normal on the day after admission and remained so. Lumbar puncture revealed the spinal fluid to be under normal pressure. The fluid gave a positive reaction for globulin; the sugar content was normal; the cell count was 22, and the total protein content was 80 mg. per hundred cubic centimeters. Bacterial culture of the spinal fluid revealed no organisms.

From the Harvard School of Public Health and the Harvard Infantile Paralysis Commission.

This study was aided by a grant from the Children's Bureau of the United States Department of Labor.

1. Fischer, A. E., and Stillerman, M.: Does an Attack of Anterior Poliomyelitis Confer Adequate Immunity? J. A. M. A. **110**:569 (Feb. 19) 1938.

Examination of the muscles showed the paralysis arising from the second attack to be mild. The abdominal muscles which had been involved in the first attack showed further paralysis, as did the quadratus lumborum on the right. The patient was discharged from the hospital eight days after admission and was subsequently observed for eight years at the clinic.

CASE 2.—*First Attack.*—B. S., aged 4 years, was admitted to a local hospital on Aug. 1, 1931—an epidemic year for poliomyelitis in Massachusetts—with a complaint of malaise, weakness of both arms and difficulty in talking of one week's duration. The illness started with vomiting and fever. On the fourth day it was noted that the patient's neck and back were stiff, and subsequently it was noted that he had weakness of his left arm and a change in his speech.

Examination at that time revealed tenderness of the muscles of the shoulders and absence of the reflexes of the left arm and the abdomen. The temperature at the time of admission was normal. When lumbar puncture was done, the spinal fluid was clear and under normal pressure. It showed an increased content of globulin and 60 cells per cubic millimeter, of which 35 per cent were monocytes and 65 per cent were polymorphonuclear cells.

The patient was first seen at the clinic of the Harvard Infantile Paralysis Commission two weeks later and at that time was found to have sensitivity of the muscles of the left shoulder, with a flaccid paralysis involving mainly the left arm and to a minor extent the right arm. The left deltoid and latissimus dorsi muscles were rated "poor." Other muscles were involved to a lesser extent. The lower extremities were not affected. Over a period of two years the involved muscles had regained considerable strength, and examination of his muscles on Aug. 3, 1933 showed little residual paralysis. The left deltoid muscle was rated "good" at this time.

Second Attack.—On Aug. 11, 1933, two years after his first attack, this patient was again admitted to the same hospital for observation. A diagnosis of acute anterior poliomyelitis was made. On August 29, eighteen days later, he was seen at the clinic of the Harvard Infantile Paralysis Commission, at which time he was unable to walk and had considerable involvement of his legs, which had not been involved in the first attack. There was considerable hypersensitivity of the muscles of both lower extremities. Examination of the muscles revealed an extensive flaccid paralysis involving the abdomen, back and both legs.

At the first examination more than half of the muscles in these areas were rated "poor." The arms were not involved in this second attack.

The pattern of recovery was typical of anterior poliomyelitis. The last examination of the muscles was made on Nov. 12, 1940. Some residual paralysis from the second attack remained.

CASE 3.—*First Attack.*—C. C. at the age of 10 months had an illness of two days' duration with pyrexia of unknown origin. This was during the summer of 1927, which was an epidemic year for poliomyelitis in Massachusetts. No weakness of the legs was noted immediately thereafter, but at the age of 18 months, when he first started to walk, it was noticed that he used his left leg poorly. When he was 19 months of age, examination at the clinic of the Harvard Infantile Paralysis Commission revealed a pronounced calcaneovalgus deformity of the left foot. Examination of the muscles showed the gastrocnemius and posterior tibial muscles on this side to be "poor," with a lesser degree of weakness of other muscles in this extremity. Other than a mild involvement of the abdominal muscles, no other paralysis was found. There was no evidence of other factors that might cause such a paralysis, such as spina bifida or lead poisoning. A diagnosis of "old anterior poliomyelitis" was made and treatment instituted. After the maximal improvement had been attained by conservative measures, transplantation of the tendons of the peroneus longus, peroneus brevis and flexor digitorum longus muscles to the os calcis was performed and a subastragalar arthrodesis was done.

Second Attack.—Eight years after the first attack, on Aug. 14, 1935, which was an epidemic year for poliomyelitis in Massachusetts, this patient was admitted to the Children's Hospital with a complaint of pains in his hands, neck and back for three days. His temperature was 102 F. Examination revealed stiffness of the neck and sensitivity of both the upper and the lower extremities. His pharynx was injected, and there was some cervical adenopathy. Lumbar puncture was done and showed a clear fluid with 170 mm. pressure, a positive reaction for globulin, a normal sugar content and a cell count of 23, with 90 per cent mononuclears. His temperature was normal after twenty-four hours and so remained. Examination of the muscles revealed definite weakness of the left arm from this attack, but no muscles were rated below "good."

A diagnosis of a second attack of anterior poliomyelitis was made, and he was discharged eight days after admission and referred to the clinic of the Harvard Infantile Paralysis Commission. The patient was last seen April 2, 1940. Some residual paralysis remained from the first attack, but the muscles involved in the second attack were all "normal" at the last examination.

CASE 4.—*First Attack.*—On Nov. 12, 1927, an epidemic year for poliomyelitis in Massachusetts, M. M., aged 10 years, became ill, complaining of chills, fever and vomiting followed by a weakness of the left leg. Examination when the child was first seen at the clinic of the Harvard Infantile Paralysis Commission, two months after the onset, revealed a hypersensitiveness of the left leg, particularly on stretching of the hamstrings and gastrocnemius, associated with flaccid paralysis of patchy distribution. The paralysis was not extensive, and no muscles were rated below "fair." There was a slight contraction of the left achilles tendon at this time. The patient was treated in the clinic, and two years later all muscles were recorded as "normal."

Second Attack.—On Aug. 26, 1931, which was an epidemic year for anterior poliomyelitis in Massachusetts, this patient had an acute illness with pain in the back of her head, stiffness of her neck and vomiting. Her physician made a tentative diagnosis of infantile paralysis, and she was referred to a hospital for patients with contagious diseases, where a lumbar puncture was done, revealing a clear fluid which was under a pressure of 120 mm. The fluid was reported as showing 200 cells per cubic millimeter, a positive reaction for globulin and a normal sugar content. At this time she had some difficulty in swallowing and her voice had a definite nasal quality. When she was seen at the clinic of the Harvard Infantile Paralysis Commission in October 1931, there remained rather widespread but mild hypersensitivity. Except for this difficulty in swallowing and in speaking, however, no further muscular involvement could be demonstrated with the second attack. One month later, the patient still had some difficulty in swallowing solids and still had a nasal voice, but both of these conditions gradually improved, so that by March 1933 there was no difficulty in swallowing and the nasal quality of her voice was barely recognizable.

COMMENT

The possible significance of reported second attacks of anterior poliomyelitis is dependent first on the certainty of the diagnosis. It is difficult to be absolutely sure of the diagnosis in both attacks, for even when detailed studies at the time of the second attack prove the presence of the disease, the nature of the first attack may still be open to question. The fact, however, that both attacks in each of the 4 cases were paralytic simplifies our problem to a certain extent.

The diagnosis of anterior poliomyelitis in our cases was based on the history and clinical examination during the acute phase, on the subsequent course of the disease and, in many instances, on findings in the spinal fluid. No virus studies were made; consequently, although we feel the diagnosis to be justified in each instance, we cannot make an unequivocal statement that all our patients had two attacks of poliomyelitis.

The factors in the individual cases which strongly suggested the diagnosis of anterior poliomyelitis in both attacks are in part outlined in the table. The nature and distribution of the paralysis in all 4 patients was such as to simplify the differential considerations. In each instance it was flaccid in type and patchy in distribution, with no recorded evidence of significant sensory disturbances. The pattern of recovery from the paralysis after each attack was typical of anterior poliomyelitis. In all except 1 instance the patient was seen at the clinic relatively soon after the initial attack, at a time when he presented positive physical signs other than the paralysis. In all cases the patient was observed at intervals between the first and second attacks as well as after the second attack.

One point that has a certain bearing on the correctness of diagnosis in the cases involved is the fact that all attacks, both first and second, occurred under circumstances epidemiologically consistent with poliomyelitis. In each instance the acute attack took place at the height of the seasonal prevalence of poliomyelitis and in a locality where the disease was prevalent at the time.

In our patients the diseases to be particularly considered in differential diagnosis were the so-called Guillain-Barré syndrome, or "infectious neuritis," and peripheral neuritis, arising from infections or from other causes. There was noth-

ing in the history or physical findings of any of our patients to suggest an infectious origin. As for the Guillain-Barré syndrome,[2] this differentiation could not be positively made in all instances, although the clinical picture of the acute illness, including the distribution of the paralysis and the subsequent course of the disease, was more characteristic of anterior poliomyelitis. The findings in the spinal fluid in those instances in which it was examined were entirely typical of anteror poliomyelitis, and in no case was the protein content extremely elevated.

In our cases the areas of the spinal cord involved in the second attack, as judged by the distribution of paralysis, were largely areas not involved in the first attack. Toomey [3] has stated that he is skeptical of second attacks and has suggested that many of the common infections may cause an increase in the paralysis by involving the few remaining peripheral nerves and their cells of origin. Since in 3 of our cases different areas of the cord were involved in the two attacks, as judged by the distribution of the paralysis, this possibility seems unlikely.

Summary of Cases

Attacks	Age, Yr.	Month	Incidence of Poliomyelitis	Interval Between Attacks, Yr.	Symptoms of Acute Attack	Muscle Hypersensitivity	Type of Flaccid Patchy Paralysis	Distribution of Paralysis	Recovery Pattern	Spinal Fluid Findings
Case 1										
First	4	September	High		Typical	Present	Severe	Legs, abdomen and back	Typical	Not examined
Second	9	August	High	5	Typical	Present	Mild	Abdomen and back	Typical	Typical
Case 2										
First	4	August	Epidemic		Typical	Present	Moderate	Arms	Typical	Typical
Second	6	August	Epidemic	2	Typical	Present	Severe	Legs	Typical	Not examined
Case 3										
First	10 mo.	Summer	Epidemic		Unrecognized acute illness	Not recognized	Moderate	Left leg	Typical	Not examined
Second	9	August	Epidemic	8	Typical	Present	Mild	Left arm	Typical	Typical
Case 4										
First	10	November	Epidemic		Typical	Present	Moderate	Left leg	Typical	Not examined
Second	14	August	Epidemic	4	Typical	Present	Mild	Bulbar	Typical	Typical

A comparison of the degree of acute illness and the amount of subsequent paralysis in the first attack with those in the second shows no constant pattern. In 1 patient the paralysis in the first attack was severe; in a second, very mild. In another patient (case 2) the paralysis of the first attack was localized and moderate in severity; that of the second attack was much more severe. In none of the 4 patients was there an extensive paralysis with both attacks.

Most of the recorded second attacks of anterior poliomyelitis have been reported as isolated cases; Fischer and Stillerman [1] have made the only effort to determine the actual incidence of second attacks. They estimated that in 3.4 cases per thousand new cases in the city of New York in 1935 the patient would be expected to have had a previous attack of poliomyelitis by chance if the first attack conferred

2. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire. Remarques sur les caractères cliniques et graphiques des réflexes tendineux, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462, 1916.

3. Toomey, J. A.: Second Attacks of Poliomyelitis, Am. J. Dis. Child. **56**:969 (Nov.) 1938.

no immunity whatsoever. Their actual ratio of secondary to primary attacks in New York for that year was 2 to 1,000. Our rate for second attacks was 4 of 6,000 patients, or 0.66 per thousand. This was not greatly different from Aycock's [4] estimate that 1 person in every 1,000 of the general population in Massachusetts will have clinically recognized anterior poliomyelitis. If we take the liberty of combining the attack rate of Fischer and Stillerman with ours, we arrive at a rate of second attacks of 1 for each 1,000 primary infections. More surveys, however, are essential before any positive conclusions can be drawn as to the real incidence of second attacks in human beings.

On the basis of the similarity of the attack rate in the general population and in people with a history of a previous infection with the disease, some investigators [1] have questioned the adequacy of the immunity induced by an acute infection. On the surface, this would seem to be the logical conclusion and is a possibility. On the other hand, it is also possible that this failure to acquire immunity from an attack of anterior poliomyelitis is a characteristic of only the exceptional person. This would seem to be the case with other common communicable diseases, in which, because of the relative ease of recognition of the acute form, it is possible to observe that persons who have had one attack rarely have a second.

How can one explain the apparent fact that the incidence of the recognized disease in the general population and in persons previously infected is so nearly alike if the majority of those infected with poliomyelitis acquire immunity? A possible explanation may be found in the work of Aycock,[5] Draper [6] and others. They have suggested that of the many people who are infected with the virus of poliomyelitis few have paralysis or clinically recognized poliomyelitis and that the factor which determines the development of paralysis lies within the host. Thus, those in whom the paralytic disease develops on contact with the virus may be considered to have a certain type of peculiar susceptibility. If this is the correct interpretation of the observed facts in poliomyelitis, a second attack rate of 1 to 1,000 would suggest that in most instances an effective immunity was produced by the first attack. In other words, of those persons who are peculiarly susceptible to the disease and in whom paralysis develops 999 out of every 1,000 acquire such resistance that second attacks do not occur. Indeed, virus neutralization tests and studies of age incidence give strong evidence that at least some immunity to the virus of poliomyelitis is widespread.

Monkeys, although probably more resistant to infection with the virus of poliomyelitis than human beings, may likewise be susceptible to a second attack.[7] Flexner [7a] was able to produce reinfections by intranasal inoculations in a high percentage of his monkeys, and within a short time of the original infection.

Different strains of the virus of anterior poliomyelitis have been reported by many investigators,[8] and it is entirely possible that second attacks of the disease in human beings may be caused by strains of the virus immunologically different

4. Aycock, W. L.: Personal communication to the authors.

5. Aycock, W. L.: Constitutional Types and Susceptibility to Paralysis in Poliomyelitis, Am. J. M. Sc. **202**:456, 1941.

6. Draper, G.: The Nature of the Human Factor in Poliomyelitis, Am. J. M. Sc. **184**:111, 1932.

7. (*a*) Flexner, S.: Reinfection (Second Attack) in Experimental Poliomyelitis, J. Exper. Med. **65**:497, 1937. (*b*) Howe, H. A., and Bodian, D.: Second Attacks of Poliomyelitis: An Experimental Study, ibid. **74**:145, 1941. (*c*) Kessel, J. F.; Stimpert, F. D., and Fisk, R. T.: Immunologic Comparison of a Los Angeles Strain of Poliomyelitis with the M. V. Strain, Am. J. Hyg. **27**:519, 1938.

8. Paul, J. R., and Trask, J. D.: Strains of Poliomyelitis Virus, J. Exper. Med. **58**:513, 1933. Kessel, Stimpert and Fisk.[7c]

from those concerned in the original infection. In general, reports suggest that reinfections in animals are less likely to occur with homologous than with heterologous strains, although certain experiments of Kessel and Stimpert [7e] suggest that susceptibility to reinfection is more dependent on the relative ability of different strains of the virus involved in the original infection to produce immunity than on the factor of homology or heterology.

In our cases, the second attacks occurred five, two, eight and four years, respectively, after the original ones. We know of no cases that have been reported which have had an interval between attacks of less than two years. Still [9] in 1930 proposed that this quiet period suggests an effective immunity for at least two years. The number of second attacks reported in the literature, however, is so small that the absence of reinfection in reported cases during this two year period could be due entirely to chance, particularly when one considers that the incidence of poliomyelitis is relatively low for a year or two after an epidemic and chance of exposure is therefore small. On the other hand, the concept of a relatively complete immunity in human beings for a period after an acute attack—as suggested by Still—followed by a partial immunity closely parallels that which has been accepted for many other diseases.

SUMMARY AND CONCLUSIONS

Four cases of apparent second attacks of anterior poliomyelitis are reported, and their possible significance is discussed. In each instance, both attacks were accompanied by paralysis.

The available data suggest that the incidence of second attacks is approximately that of the incidence of recognized first attacks in the general population, although this cannot be concluded at this time. Determination of the true incidence of second attacks must depend on summary data from a larger number of cases than have been recorded in the literature. Incidence figures, where available, should be reported.

The average interval between attacks in our series was five years, with the shortest interval two years. In no accepted cases of second attacks reported in the literature has there been less than this two year interval.

Reports of second attacks of anterior poliomyelitis should be reviewed critically, since proof of the disease is difficult. No absolute conclusions can be drawn at this time regarding the immunologic implications of reported second attacks.

Second attacks of anterior poliomyelitis seem to occur often enough that the possibility of that disease must be considered in differential diagnosis, even if the patient has had a previous attack.

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9. Still, G. F.: Second Attacks of Acute Poliomyelitis, and the Minimal Duration of Immunity, Arch. Dis. Childhood **5**:295, 1930.

PSEUDOREACTIONS TO TUBERCULIN

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While the tuberculin patch test was under clinical trial, numerous publications appeared which evaluated the patch test by comparison with the Mantoux test. This procedure of evaluation appeared unassailable. The Mantoux test had been accepted as the standard test seemingly of known value. One was to express in terms of this "known value" the as yet unknown value of a new test. From this assumption it was only logical to blame the new test for any discrepancy between the results of the two tests. Since the reliability and infallibility of the Mantoux test were taken for granted, it was permissible to term a nonconforming reaction to a patch test as a "false" positive or "false" negative reaction.

Doubts as to the infallibility of the Mantoux test have been frequently but timidly expressed in the past; nobody likes to meddle with conventional values and standards. It is noteworthy, however, that the continent on which the Mantoux test originated did not accept it as standard, explicitly because it engenders too many pseudoreactions. It may well be that the conjectural superior feature of the Mantoux test, namely the fact that it elicits more positive reactions than other tests, is its weakness. Recently two valuable contributions in the literature substantiated this opinion.

Furcolow, Hewell, Nelson and Palmer,[1] of the United States Public Health Service, determined the sensitivity to tuberculin of various age groups of infected, as well as of noninfected, noncontact children with intracutaneous injections of gradually increasing amounts of purified protein derivative. The lowest dose used was 0.00000000001 mg. and the highest 1.0 mg. Only a few pertinent facts of this most comprehensive study may here be mentioned:

1. In a group of 553 nontuberculous children aged from 6 to 19 years a steady increase in the accumulated percentage of positive reactors was found with increase of the dose of tuberculin. About 20 per cent of the children had positive reactions to the first test dose (0.00002 mg.) of purified protein derivative, 50 per cent at the level of the second test dose (0.005 mg.) and 96 per cent to the largest dose used, 1.0 mg.

2. Of another group of 116 nontuberculous and noncontact infants and young children from birth through 6 years of age, a high percentage reacted to tuberculin if sufficiently large doses were injected. Even among infants under 6 months of age, 71.9 per cent reacted to 1.0 mg. of purified protein derivative.

3. The results observed in these 116 noninfected infants and young children together with those in 248 children 6 to 19 years of age who did not show any tuberculous lesion and had no known history of contact with tuberculosis are

†Dr. Ripps died Oct. 28, 1942.

From the St. Walburga's Orphanage, Roselle, N. J.

1. Furcolow, M. L.; Hewell, B.; Nelson, W. E., and Palmer, C. E.: Pub. Health Rep. 56:1082, 1941.

charted in figure 3 of Furcolow's paper. Calculated from this figure, about 5 per cent of the children between 6 months and 3 years of age, more than 20 per cent of the children between 4 and 6 years and more than 40 per cent of the children between 6 and 19 years reacted at the level of the second strength dose of purified protein derivative.

4. Furcolow and co-workers assumed that reactions which are obtained only to large doses of purified protein derivative may be unspecific and not due to tuberculous infection.

Smith, Faulkner and Cordi [2] published a similar study of reactions to old tuberculin. The highest dose these authors used was 10 mg. of old tuberculin, which is approximately only one twentieth of the strength of 1.0 mg. of purified protein derivative used as the highest dose by Furcolow and co-workers. Of 217 children under 13 years of age who did not react to 0.1 mg. of old tuberculin, 32, or about 15 per cent, showed peculiar reactions to 10 mg. and 15, or about 7 per cent, to 1 mg. of old tuberculin. Those reactions were characterized by rapid fading, and their occurrence increased with the amount of old tuberculin used; they were termed by Smith and co-workers "false positive reactions, or pseudo-reactions," probably resulting from sensitivity to broth.

Reactions to Tuberculin

Test	Number of Children Tested	True or False Positive Reactions After 24 Hr.	After 48 Hr.	After 72 Hr.	After 96 Hr.
Patch	88	..	5	5	5
Mantoux (1 mg. old tuberculin)	83*	..	10 (12%)	4 1 ?	0 2 ?
Mantoux (10 mg. old tuberculin)	72†	23 (32%) 13 ?	6 (8%)	..	1 1 ?

* Negative reactors to the tuberculin patch test.
† Negative reactors to the patch test and to the Mantoux test with 1.0 mg. of old tuberculin.

EXPERIMENTAL PROCEDURE

Independently from Smith and his co-workers,[2] we carried out similar experiments with a group of 88 orphans between 6 months and 4 years of age. Only 4 of these children had a known contact with tuberculosis, and none of them showed any sign of active tuberculosis.

All children were first tested with the tuberculin patch test.[3] Only 5 showed a positive reaction. The remaining 83 negative reactors to the patch test were retested with the Mantoux test with 1.0 mg. of old tuberculin. At the forty-eight hour reading, 10, or 12 per cent, of these 83 children showed a cutaneous reaction which will be discussed later. Seventy-two children who at the forty-eight hour reading were negative reactors to the Mantoux test with 1.0 mg. of old tuberculin were retested with 10 mg. Thirty-six, or 50 per cent, of these 72 children showed some sort of reaction and 23, or 32 per cent, a pronounced cutaneous reaction after twenty-four hours. The majority of these reactions faded within the next twenty-four hours, and only 6, or 8 per cent, remained positive at the forty-eight hour reading. The results are tabulated in the accompanying table.

These results call for more detailed description. The 5 positive reactions to the patch test were present at the forty-eight hour reading and became more distinct

2. Smith, C. A.; Faulkner, W. H., and Cordi, J. M.: New England J. Med. **225**:1008, 1941.
3. Lederle Laboratories, New York, supplied the materials for the tests.

during the subsequent forty-eight hours. Three of the 5 positive reactors had a known history of contact. Roentgenograms were made for the 5 positive reactors to the patch test; 3 of them showed conditions consistent with arrested childhood type tuberculosis.

Of the 83 negative reactors to the patch test, 10 showed at the forty-eight hour reading a positive reaction to the Mantoux test with 1.0 mg. of old tuberculin. Though these reactions had to be interpreted as positive according to diagnostic standards, there was some doubt as to their significance. They faded rapidly during the following twenty-four hours, and 5 reactions had completely disappeared at the seventy-two hour reading, in contrast to true tuberculin reactions. The peculiarity of the cutaneous manifestations themselves became more conspicuous with the use of still higher concentrations of tuberculin.

Of the 72 children who were retested with 10 mg. of old tuberculin, 23 showed at the twenty-four hour reading a reaction consisting of extensive erythema and of swelling which was edema rather than induration. Seventeen of these reactions had completely faded twenty-four hours later, at the forty-eight hour reading. At this time only 6 reactions remained, and they were characterized by extensive erythema, edema and itching, some appearing like urticaria with some central blisters. Only 1 of these reactions was still visible at the ninety-six hour reading. In addition to these 23 pronounced cutaneous reactions, there were 13 weaker reactions at the twenty-four hour reading which did not entirely comply with diagnostic standards for a positive reaction. They consisted either of erythema of more than 1 cm. in diameter or of reddening and swelling; there was no induration. All these weaker reactions had faded at the forty-eight hour reading.

We made 9 leukocyte counts of blood obtained from punctures of the skin in the area of reaction caused by the intracutaneous injection of 10 mg. of old tuberculin. Of these 2 showed a slightly increased number of white cells, with a normal differential count. The others showed a normal number of leukocytes, with a slight increase of the polymorphonuclear cells in 2. Helmreich [4] in his extensive studies on local blood counts found a relative lymphocytosis with a normal white cell count in the area of reaction to a Pirquet test in clinically healthy children who had shown a weak positive reaction to a tuberculin test and had arrested primary tuberculosis. In our cutaneous reactions caused by high concentrations of tuberculin no such relative lymphocytosis was observed. Helmreich's local blood count might therefore be an aid in differentiating between reactions and pseudoreactions to tuberculin.

COMMENT

Is it permissible to speak of pseudoreactions to tuberculin?

In our experiments there were 72 orphans between 6 months and 4 years of age with no known history of contact with tuberculosis and with negative reactions to a patch test as well as to a Mantoux test with 1.0 mg. of old tuberculin. Those criteria are generally regarded as sufficient to rule out a tuberculous infection. If 32 per cent of these nontuberculous young children show a distinct cutaneous reaction, with swelling of more than 10 mm. in diameter and with a large erythema, twenty-four hours after the intracutaneous injection of 10 mg. of old tuberculin, doubt as to the significance of such reactions is justified, if not inevitable. A 32 per cent incidence of tuberculous infections among noncontact children between 6 months and 4 years of age would by far exceed the expectation for any population group. Infected children of this low age group with a sensitivity to tuberculin

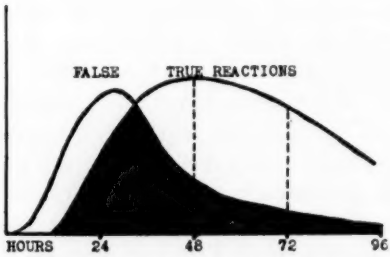
4. Helmreich, E.: Klin. Wchnschr. **8**:1254, 1929. Helmreich, E., and Neumann, A.: Monatschr. f. Kinderh. **54**:255, 1932.

so low that they react only to 10 mg. of old tuberculin are—if the condition occurs at all—an extreme rarity. To assume that 32 per cent of the children in our experiment represented such a rarity would be illogical. We do not hesitate to state that these 32 per cent of children were in all probability not infected with tuberculosis and that their cutaneous reactions to high concentrations of tuberculin were pseudoreactions.

Pseudoreactions to tuberculin differ from true positive reactions in certain characteristics:

1. Pseudoreactions result only from higher concentrations of tuberculin, exceeding 0.1 mg. of old tuberculin or 0.0001 mg. of purified protein derivative.

2. They appear and fade more rapidly, having their maximum size at about twenty-four hours. The majority of pseudoreactions disappear after forty-eight hours, when specific reactions to tuberculin attain their maximum size. Between forty-eight and ninety-six hours, true reactions to tuberculin retain their size or decrease slowly; the majority of pseudoreactions have completely disappeared or disappear rapidly during this period. The chart schematizes the average course of both types of reactions. The curve of pseudoreactions forms a steep elevation; that of true positive reactions, a broad plateau. Both curves are overlapping,



Course of true and false positive reactions to intracutaneously injected tuberculin.

particularly between twenty-four and forty-eight hours. At this period it is more difficult to distinguish between true and false positive reactions than at forty-eight hours or at seventy-two hours, when most of the pseudoreactions have faded and most of the specific reactions are still distinct. Schick [5] obtained similar curves from his observations of true and false reactions to diphtheria toxin.

3. Pseudoreactions appear as a diffuse erythematous swelling, in contrast to true positive reactions, which appear as a more sharply limited, definite induration with a surrounding erythema.

Our results confirm qualitatively the observations of Smith, Faulkner and Cordi.[2] The percentage difference may be due to differences in age group, age distribution, character of the groups, tuberculin preparations and perhaps other factors.

However, both the percentage figures of Smith and his associates and ours obtained with old tuberculin remain far below those obtained by Furcolow and his associates [1] with purified protein derivative. The latter authors reported on one group of 65 children aged 6 months through 3 years, residents of two foundling homes, having no history of contact with and no roentgenographic evidence of pulmonary tuberculosis. This group was similar to ours, though the children were slightly younger and had a more definitely negative history of tuberculosis. Never-

5. Schick, B.; von Gröer, F., and Kassowitz, K., in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1933, vol. 13, pt. 2, p. 503.

theless, we found at the forty-eight hour reading only 20 per cent of pseudoreactions to 1.0 and 10 mg. of old tuberculin. Furcolow and co-workers found in their similar group an accumulated percentage figure of more than 50 per cent of pseudoreactions to 0.05 mg. of purified protein derivative, which corresponds biologically with 10 mg. of old tuberculin, and of 73.8 per cent to 0.1 mg. of purified protein derivative.

It therefore appears justified to state that purified protein derivative causes more pseudoreactions than biologically corresponding concentrations of old tuberculin.

This fact is not in favor of Smith, Faulkner and Cordi's [2] assumption that pseudoreactions may be due to sensitivity to broth. Purified protein derivative is derived from tubercle bacilli grown in a nonproteinic synthetic medium and does not contain any broth; nevertheless corresponding doses of purified protein derivative elicit a considerably higher percentage of pseudoreactions than do doses of old tuberculin. Not broth but tuberculoprotein itself seems to be responsible for the majority of pseudoreactions caused by old tuberculin as well as by purified protein derivative. For tuberculoprotein is the only substance which both preparations have in common; purified protein derivative contains nothing but tuberculoprotein. Only with the assumption that tuberculoprotein is the offending substance can we understand why purified protein derivative causes more pseudoreactions; it contains the offending substance in a purer form than does old tuberculin. Old tuberculin contains in addition to tuberculoprotein other substances. It may well be that these "impurities," such as broth, occasionally elicit unspecific cutaneous reactions in allergic persons. But, taken on the whole, those "impurities" of old tuberculin seem to be less offending, less irritating and less apt to produce pseudoreactions than tuberculoprotein [6] itself.

It seems reasonable to assume that tuberculoprotein, like other foreign proteins, is a primary irritant to the epidermal tissue. The occurrence of pseudoreactions depends on the concentration of this foreign protein and on the individual sensitivity or irritability.

We injected intracutaneously 0.1 cc. of sterilized cow's milk into a few nonallergic, tuberculin-negative reactors. The resulting cutaneous reactions resembled pseudoreactions to tuberculin in every respect. The maximum size of the reactions was attained within twenty-four hours. They consisted of an extensive edematous erythema and faded rapidly within the subsequent twenty-four hours.

Distinctly different biologic processes are involved in pseudoreactions and in true positive reactions to tuberculin. According to von Pirquet, infection with tubercle bacilli results in the formation of specific antibodies. Whenever tuberculin comes into contact with these antibodies, toxic reaction products result, which von Pirquet called apotoxins. A positive reaction to tuberculin is an allergic vascular reaction to apotoxin. At the site of an intracutaneous injection of tuberculin, apotoxin is not formed immediately but is gradually released over a period of time, which explains the prolonged course of the reaction, illustrated as a plateau in the chart. On the other hand, high concentrations of tuberculin intracutaneously injected into persons nonallergic to tuberculin act as an immediate primary irritant which the tissues rapidly dispose of.

Besides a general irritability of the nonallergic epidermal tissue to high concentrations of tuberculoprotein, a variable individual sensitivity may play a role.

6. The term "tuberculoprotein" is here used as comprising tuberculin as well as proteinic substances of the tubercle bacillus body. No evidence is available indicating that pseudoreactions are caused only by proteins of the tubercle bacillus body.

Furcolow and co-workers clearly demonstrated that sensitivity to tuberculin and percentage of pseudoreactions tend to increase with age. This phenomenon may in part be explained, as was done by Furcolow, on the basis of increasing opportunities for unknown contact with the tubercle bacillus. We should expect that increasing contact with living tubercle bacilli would result in increasing percentages of tuberculous infections and true positive reactions to small amounts of tuberculin. It appears, however, that pseudoreactions to only high concentrations of tuberculin also increase with increasing age. This is in line with the observations of Schick, von Gröer and Kassowitz [5] that sensitivity to bacterial proteins increases with age.

The question arises whether the tuberculin patch test may also cause pseudoreactions. There will be a few persons with allergy to adhesive mass or to broth who will manifest pseudoreactions, which can be easily distinguished from specific reactions to tuberculin with the aid of the control patch. There will be another few persons, particularly when the test is made during summer or if they are persons with excessive perspiration, on whom a faint miliaria rash appears at the site covered by the patches. This is an inflammation about the sweat glands caused by perspiration. It is not indurated, is less elevated and fainter than a true reaction to tuberculin and decreases rather than increases in intensity after removal of the patch test strip. These rare miliaria rashes have been misinterpreted as weak or questionable positive reactions. Experience may prevent this error. We did not observe at the ninety-six hour reading pseudoreactions to the patch test caused by tuberculin and simulating distinctly positive reactions. Other investigators arrived at a similar conclusion. Smith, Faulkner and Cordi [2] stated: "No patient who failed to react to the Mantoux test gave any reaction to the patch, so that the latter test cannot be suspected of producing false positive results." Only small amounts of tuberculin are percutaneously absorbed, sufficient to elicit a positive reaction in an infected person with tuberculin allergy. High concentrations of tuberculin which are required to produce pseudoreactions do not seem to penetrate the skin.

On the other hand, what have been designated as "false negative" reactions to a patch test by a few investigators [7] who used the Mantoux test with high concentrations of tuberculin for comparison may well have been misnamed. It appears reasonable to assume that a good deal of their "positive" Mantoux reactions to 1.0 mg. or more of old tuberculin and to the second test strength of purified protein derivative were pseudoreactions.

The present concept of pseudoreactions by no means impairs the value of intracutaneous tuberculin tests. It may prevent misinterpretations; it may eliminate the stigmatizing of noninfected children, which brings as much distress to the parents as the discovery of a true tuberculous infection. It teaches physicians to attribute significance only to those, even weak, reactions which are elicited by the smaller doses of tuberculin, not exceeding 0.1 mg. of old tuberculin or 0.0001 mg. of purified protein derivative. Reactions caused by higher concentrations, e. g. 1.0 mg. of old tuberculin or second test strength of purified protein derivative, should be interpreted with caution. They may be reread at seventy-two hours. Rapid fading between forty-eight and seventy-two hours is more suggestive of a pseudoreaction; persistence of size and induration are more indicative of a true reaction to tuberculin. Infected children with low sensitivity to tuberculin, reacting only to 1.0 mg. or more of old tuberculin, are usually sensitized by preceding injections of tuberculin and may react positively to subsequent smaller doses. Noninfected pseudoreactors usually do not show this phenomenon.

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7. Kereszturi, C.: Am. Rev. Tuberc. **54**:94, 1941.

If the clinical use of doses of tuberculin exceeding 0.1 mg. of old tuberculin were abandoned, a case of arrested tuberculosis might occasionally be missed but confusion and diagnostic errors for a much higher percentage of children would be avoided.

SUMMARY

Intracutaneous injection of 1.0 mg. or more of old tuberculin frequently causes pseudoreactions in children not infected with tuberculosis.

Purified protein derivative seems to cause more pseudoreactions than corresponding doses of old tuberculin.

The percentage of pseudoreactions increases with the concentration of tuberculin and the age of the subject.

The majority of pseudoreactions are not caused by broth but by tuberculoprotein.

Pseudoreactions appear and fade more rapidly and show less distinct induration than true reactions to tuberculin.

The patch test causes, if any, less pseudoreactions than the Mantoux test with more than 0.1 mg. of old tuberculin.

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TOTAL AND FRACTIONAL BLOOD LIPID LEVELS IN THE NEPHROTIC SYNDROME

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The blood chemistry of the nephrotic syndrome is characterized by abnormal plasma protein levels and by hyperlipemia. The latter, despite years of study, remains one of the more obscure features of this disease. I should like, therefore, to present and to comment on an example of unusually severe nephrotic hyperlipemia in a patient whose total plasma lipid and all significant fractions thereof have been followed over a nine month period beginning soon after the onset of his illness.

In the following report the results have been summarized in relation to events of the patient's clinical course and I have indicated a few correlations which would seem to merit further study.

These determinations are part of an extended survey, not yet complete, of abnormal blood fat levels in certain diseases of childhood. With the aid of the same modified Bloor technic [1] which is used in the present study, normal ranges for total and fractional blood lipid levels in children are also being determined for purposes of comparison.

REPORT OF A CASE

This patient's illness started as an apparently pure nephrosis and has exhibited throughout severe nephrotic characteristics. In addition, however, microscopic hematuria (conceivably related to a chronic sinusitis) has made its appearance during the course of the disease and has gradually increased in the absence of hypertension, progressive retention of nitrogen or other signs of glomerulonephritis. This observation adds interest to the persisting high levels of lipid in the blood. The clinical history is as follows:

E. K. was admitted to the hospital in August 1941, at the age of 4½ years, with a complaint of a slowly progressive edema of about two months' duration, with ascites and oliguria during the last three weeks of this time. His parents had noticed no cold or other illness for at least two months preceding the onset of the edema.

On physical examination he did not seem seriously ill but presented a pronounced generalized edema with ascites, and also edematous injected tonsils. His blood pressure was 114 systolic and 74 diastolic. Laboratory observations included: an albumin content in the urine of 8 Gm. per liter, a urinary specific gravity of 1.028 to 1.040 and occasional hyaline casts but no red blood cells in the urine. Total plasma proteins were 3.1 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1. The nonprotein nitrogen content of the whole blood was 38 mg. per hundred cubic centimeters. The nose and throat contained type XVI pneumococci. There was no fever.

Though diuretics together with transfusions of blood and plasma were generously employed, his edema gradually increased, so that three paracenteses were required during the first month. The course of his illness was further complicated at the end of the month by a type VI pneumococcus cellulitis of the abdomen and legs with bacteremia, which responded in about ten days to treatment with sulfathiazole and specific serum. The throat contained no pneumococci at that time, nor was there any pulmonary involvement. There was moderate fever.

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1. Bloor, W. R.: J. Biol. Chem. **77**:53, 1928; **24**:227, 1916; **82**:273, 1929. Boyd, E. M.: ibid. **101**:323, 1933.

	1 10/16/41	2 1/19/42	3 3/3/42	4 3/19/42	5 4/3/42	6 5/22/42	7 6/12/42
Blood Fats							
Phospholipid *	375	510	785	940	670	995	850
Total cholesterol *	860	1,060	2,120	1,445	950	1,735	1,020
Free cholesterol *	285	270	925	670	340	745	590
Combined (ester) cholesterol †	575	790	1,195	775	610	990	1,030
Cholesterol ester fatty acids †	400	555	835	545	425	695	705
Cholesterol esters †	975	1,345	2,030	1,320	1,035	1,685	1,735
Neutral fat †	250	485	3,060	2,505	1,055	1,970	1,985
Total lipid †	1,885	2,610	6,800	5,435	3,100	5,395	5,160
Other Laboratory Data							
Nonprotein nitrogen (mg./100 cc.)	28	35	40-26	50-34	—	—	33
Albumin/globulin	1.9/1.8	0.8/2.6	1.2/2.1	0.4/2.0	—	0.8/2.0	0.7/2.9
Blood pressure	106/66	108/60	—	110/80	—	120/80	122/84
Microscopic hematuria	None	Rare	Few, constantly	Few, constantly	"Many"	"Occasional"	6 to 8/hpf
Addis count (red cells in millions)	6.65	0.45 (1/23)	51 (3/1)	15.2 (3/22)	196 (4/3)	100 (5/28)	—
Albumin (Gm./100 cc.)	3+	3 to 4+	4+	2 to 4+	3+	3 to 4	4+
Clinical Course							
Edema	Gradual increase 1st 4 mo.; recent decrease	Stationary 3 mo.; recent gradual increase	Gradual increase	Gradual increase	Persisting, moderate	Temporary remission; then gradual increase	Rapid increase
Fever	1 month ago	Slight, accomp.	None	None	Slight with dyspnea, rales	None	None
Complications	Pneumococcic cellulitis 1 month ago	Infection of respiratory tract and possible peritonitis	None	None	Slight with dyspnea, rales	None	None
Therapy	Plasma transfusions; paracenteses (3); urea; salt-free, high protein diet	Diet only	Diet; transfusions	Diet; paracentesis 3/10 with continued drainage	Diet; sulfathiazole	Diet only	Diet; paracentesis (6/10)

Normal levels as determined to date

Total lipid	Range 500-750;	average 650	
Phospholipid	Range 145-265;	average 200	
Total cholesterol	Range 130-275;	average 210	
Combined (ester) cholesterol	Range 75-190;	average 125	
Free cholesterol	Range 40-155;	average 80	
Cholesterol esters	Range 130-330;	average 210	
Neutral fat	Range 60-200;	overage 100	

* Values directly determined.
† Computed values.

Severe diuresis with almost complete loss of edema followed this illness: the albuminuria, however, did not improve; the level of plasma proteins remained low, and the fluid, which soon re-formed, persisted.

Discharged after ten weeks in the hospital, he remained at home in bed for three months with his condition about stationary; he then returned with a history of a recent cold, fever of mild degree and abdominal symptoms which suggested peritonitis but subsided harmlessly. He has since remained in the hospital; his edema has been constant except for a brief spontaneous remission in April 1942, which immediately followed a febrile infection of the respiratory tract.

Serial Addis counts have shown a progressive increase in red cells in the urinary sediment. Other urinary findings, the nonprotein nitrogen content of the blood, the level of plasma proteins, the blood pressure and the physical status have changed little. In spite of a reasonably good appetite, his general nutrition is only fair. Since diuretics proved ineffective, therapy has consisted largely of transfusions of blood or plasma together with a salt-free, high protein diet and paracenteses, of which two have been required during the last six months.

In the table are summarized the patient's total and fractional values for plasma lipids together with his clinical course and the therapy employed.

RESULTS

It will be noted, first, that the maximum values for plasma lipids obtained, particularly those for total lipid (6.6 Gm. per hundred cubic centimeters) and for total cholesterol (2.0 Gm. per hundred cubic centimeters); these are among the highest values reported for the nephrotic syndrome. Leiter [2] cited from the earlier literature values for total cholesterol of 0.9 Gm. per hundred cubic centimeters for children and of 1.2 Gm. for adults; a total cholesterol content of 2.3 Gm. per hundred cubic centimeters has more recently been reported.[3]

A second point of interest is the considerable fluctuation in all values, particularly their sharp rise in the period between determinations 2 and 3 and the equally sharp fall which occurred between determinations 3 and 5. Inasmuch as lipid levels in nephrosis are usually found to reflect the degree of nephrotic activity,[4] it is instructive to observe that here, likewise, the period of elevation of lipid content paralleled a period of clinical exacerbation, the most striking evidence of which was gradually increasing edema; similarly, the subsequent lower values for lipids were obtained during the spontaneous remission with severe diuresis which followed a febrile infection of the upper respiratory tract. It was not found possible to correlate the variations of plasma lipids with any of the individual nephrotic symptoms or with the use of any specific therapeutic measure.

I have attempted to determine which of the plasma lipid fractions are principally responsible for the rise and fall of the total values. In doing so, I have observed certain differences between the early and later periods of the illness, namely (chart 1):

1. In the determination made on Oct. 16, 1941, relatively early in the disease, cholesterol appears to have been responsible for the bulk of the elevation of total lipid; the rise in neutral fat, on the contrary, was not remarkable, this fraction comprising only one seventh of the total lipid.

2. Five months later (March 3, 1942) the neutral fat had risen disproportionately, to constitute nearly half of the 6 Gm. of total lipid per hundred cubic centimeters, with cholesterol representing about one third.

3. The later studies (determinations 3 to 7) suggest that neutral fat once elevated tends to remain high while cholesterol varies much more readily.

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2. Leiter, L.: Medicine **10**:193, 1931.

3. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1939, p. 387.

4. Leiter,[2] p. 200.

These changes in lipid pattern in the course of the disease find an interesting parallel when these values are compared with those of 2 other patients with the nephrotic syndrome, one set obtained shortly after onset of the disease and the other during the third year of the patient's illness (chart 2). It will be seen that the total and fractional values in the early stage are close to those of the first determination of this study, with similar high cholesterol and low neutral fat levels. In the late stage, however, as in determination 3 of this series, half of

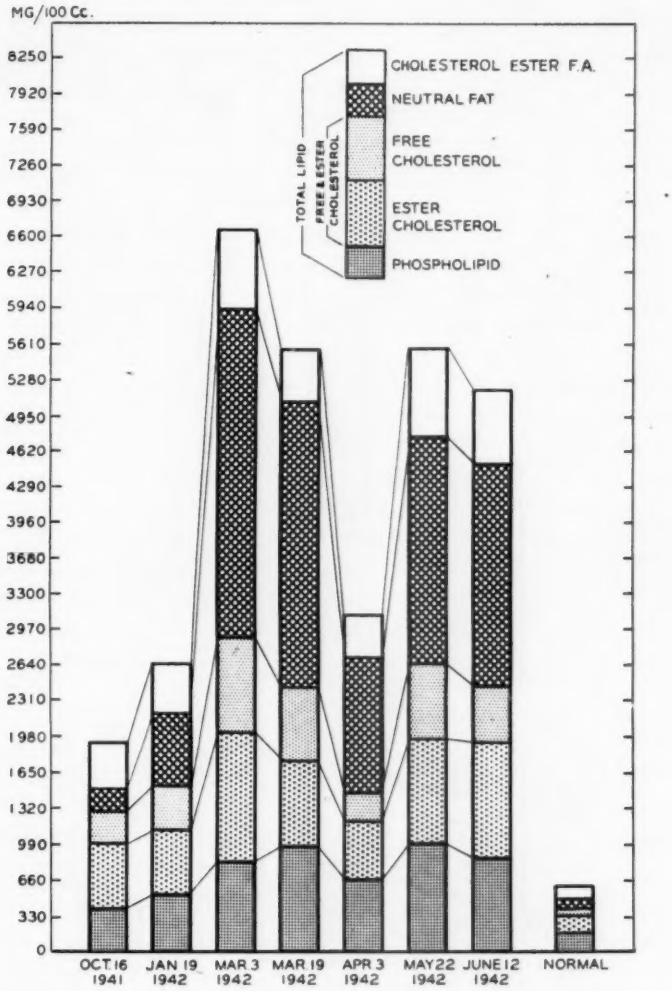

Chart 1.—Changing total and fractional lipid levels in the plasma during progress of the nephrotic syndrome.

the large amount of total lipid is composed of neutral fat, while the cholesterol represents a smaller proportion of the total.

As other observers have previously pointed out,[5] the ratio of free cholesterol to combined (ester) cholesterol remains relatively constant throughout.

Finally, it is interesting to note that the important phospholipid fraction maintains throughout a fairly constant (and normal) relation to the total lipid.

5. Hahn, A., and Wolff, E.: Ztschr. f. klin. Med. **92**:373, 1921; cited by Leiter,[2] p. 195. Page, I. H.; Kirk, E., and Van Slyke, D. D.: J. Clin. Investigation **15**:101, 1936.

Although no obvious clinical significance can be claimed for it, I should like to comment on an unusual property of this patient's blood. After observing accidentally that his blood had a distinct tendency toward spontaneous hemolysis in vitro, I learned with interest of the experiments of Johnson and his associates.[6] These investigators found that normal serum rendered hyperlipemic by feeding fat possesses increased hemolytic power and suggested that this property may be related to the free fatty acid and soap content of the increased amount

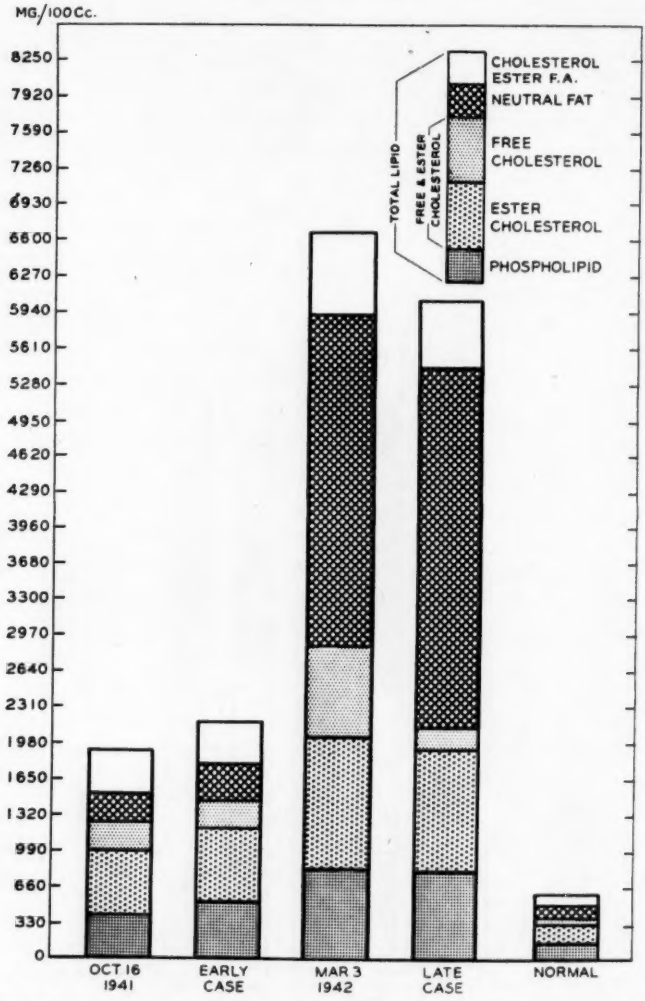

Chart 2.—Lipid levels in the plasma of E. K. compared with those of a patient in an early stage of the nephrotic syndrome and with those of a patient in a late stage.

of chyle in blood under these conditions. The hemolytic properties of fatty acids and soaps have previously been observed and related to the effect of these substances on permeability of the cell membrane.[7] Inasmuch as fatty acids and

6. Johnson, V., and Freeman, L. W.: Am. J. Physiol. **124**:466, 1938. Longini, J.; Freeman, L. W., and Johnson, V.: Federation Proc. **1**:51, 1942. Dr. Johnson checked this patient's blood for hemolytic power by the method of Johnson and Freeman, with results which appeared to confirm my observation.

7. Jacobs, M. H., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1935, vol. 4, p. 6. Horber, R.: ibid., 1932, vol. 1, p. 7.

soaps are included in the plasma lipid fraction termed "neutral fat," it is of some significance that this fraction was greatly elevated in the patient under consideration as well as in a second nephrotic patient, whose blood also showed increased hemolytic tendencies.

COMMENT

Because fat plays a conspicuous part in the abnormal blood chemistry and the pathologic changes in the kidneys in the nephrotic syndrome, an adequate explanation of its role in the pathogenesis of this disease would be of obvious value. No such explanation is as yet available. Recent research has brought but little support to the view that nephrosis is a generalized metabolic disease with the lipid disturbance as one of its manifestations.[8] A current theory which has received some experimental support regards the hyperlipemia as secondary to the low plasma protein level resulting from albuminuria, which may, in turn, be due to increased glomerular or tubular permeability,[9] as indicated in the following scheme:

Albuminuria → low plasma protein ——↗ edema [10]
↘ hyperlipemia

This interpretation is compatible with the modern view that the high lipid content of the renal tubules in a nephrotic kidney results from deposition of excess blood fat rather than from fatty tubular degeneration.[11]

It is difficult to see why a low level of plasma protein should lead to a high level of plasma lipid. The attractive suggestion that fat may be mobilized to compensate for a deficit of plasma albumin in maintaining the colloid osmotic pressure has not yet been substantiated experimentally.[12] There is evidence [13] that in nephrosis the fatty acids of the blood are more highly saturated than normal, which suggests that not all of the circulating fat may have gone through the normal processes of desaturation in the liver. In this connection, I should like to investigate the possibility that deficiency in plasma protein may interfere with the mode of transportation and subsequent metabolism of food and depot fat.[14]

920 East Fifty-Ninth Street.

8. Epstein, A. A.: Am. J. M. Sc. **163**:167, 1922; Thyroid Therapy and Thyroid Tolerance in Chronic Nephrosis, J. A. M. A. **87**:913 (Sept 18) 1926.
9. Bell, E. T.: Am. J. Path. **5**:587, 1929. Fahr, G.: Am. J. M. Sc. **194**:449, 1928.
10. Fishberg,[3] p. 375.
11. Leiter,[2] p. 201.
12. Fishberg,[3] p. 388.
13. Ling, S. M., and Liu, S. H.: Chinese J. Physiol. **2**:157, 1928.
14. Bloor, W. R.: Physiol. Rev. **19**:573, 1939.

Case Reports

AGENESIS OF LUNG IN AN INFANT

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Major anomalies are less frequent in the respiratory system than in the kidneys, genital organs or digestive tract. In over 10,000 necropsies at the New York Hospital, including many performed on newborn infants, there has been no previous instance of absence of a lung. Ellis [1] stated that Théremin found 2 cases in the records of 30,000 autopsies performed at a foundling hospital. Schmit [2] and Allen and Affelbach [3] reported fetuses with absence of both lungs, but this condition seems exceptionally rare and is of course of no clinical significance.

Deficiency of a lung has been classified as of three types by Schneider.[4] In type 1, there is no trace of a bronchus—true aplasia of the lung and bronchus. In type 2, the bronchus is represented by a blind pouch or a nodule of cartilage and fibrous tissue and there is no pulmonary tissue—aplasia of the lung. In type 3, the main bronchus is normal in size and shape and ends in a fleshy structure—extreme hypoplasia of the lung. The third type may be impossible to differentiate from secondary retraction of a previously expanded lung (Müller [5]) and will not be considered further. The literature of agenesis of the lungs has been reviewed by Ellis [1] and Hurwitz and Stephens [6] and more recently by Madigan [7] and Castellanos and Pereiras.[8] About 52 cases of complete absence of one of the lungs have been adequately described in the literature (including instances of Schneider's types 1 and 2). Of this number there are 31 in which there was no rudiment of a bronchus (Schneider's type 1). In this group the left lung with its bronchus was absent 17 times and the right 14 times.

The majority of authors either have described absence of a lung as seen at necropsy (12 times in adults) or have, on the other hand, presented a clinical report on a living patient.[9] In a case of extreme hypoplasia of a lung (Schneider's

From the Departments of Pathology and Pediatrics, New York Hospital and Cornell University Medical School.

1. Ellis, A. G.: Congenital Absence of Lung, Am. J. M. Sc. **154**:33, 1917.
2. Schmit, H.: Ein Fall von vollständiger Agenesie beider Lungen, Virchows Arch. f. path. Anat. **134**:25, 1893.
3. Allen and Affelbach: Congenital Absence of Both Lungs, Surg., Gynec. & Obst. **41**:375, 1925.
4. Schneider, P.: Die Missbildungen der Atmungsorgane, in Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1900-1913, vol. 3, pt. 2, pp. 817-822.
5. Müller, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, pp. 539-548.
6. Hurwitz, S., and Stephens, H. B.: Agenesis of the Lung, Am. J. M. Sc. **193**:81, 1937.
7. Madigan, D. G.: A Case for Discussion with Special Allusion to Congenital Absence of Lung, Tubercle **22**:144, 1941.
8. Castellanos, A., and Pereiras, R.: Pulmonary Agenesia: Report of Three Cases, and General Review, Bol. Soc. cubana de pediat. **14**:268, 1942.
9. (*a*) Van Loon, E. L., and Diamond, S.: Congenital Absence of Right Lung, Am. J. Dis. Child. **62**:584 (Sept.) 1941. (*b*) Castellanos and Pereiras.[8]

class 3) [10] and in 2 cases of absence of a lung,[11] a definite diagnosis of the condition was made during life, with confirmation at necropsy. The following case of agenesis of a lung in a 2 month old girl is presented because of the clinical points of interest and confirmation of the clinical findings at autopsy.

REPORT OF A CASE

The patient was the first child of healthy parents and was delivered normally. From birth, a gurgling sound was noted with respiration, and on crying there was pronounced retraction of the sternum and ribs. No cyanosis or fever or any other signs or symptoms of abnormality were noted. She was admitted to the pediatric service of Dr. S. Z. Levine when 6 weeks old. On physical examination, in addition to the aforementioned observations,

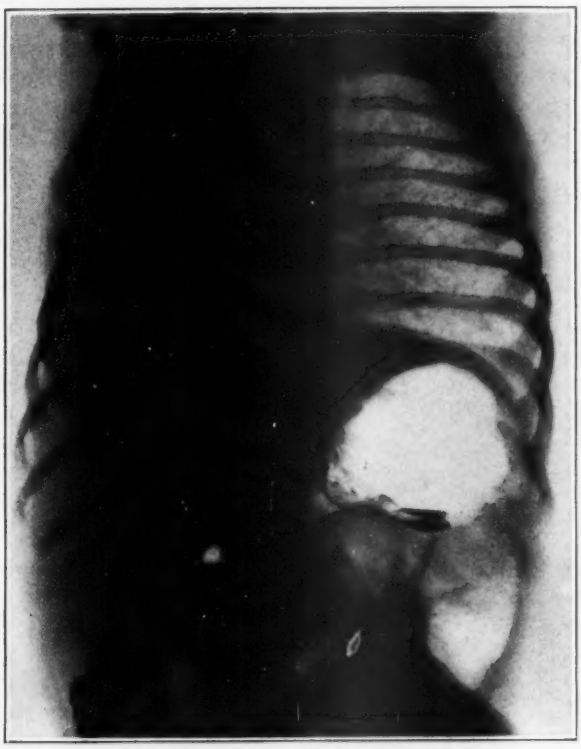

Fig. 1.—Roentgenogram made during life, showing continuity of the shadows cast by the heart in the right side of the thorax and the liver. The left lung shows evidence of hyperventilation. There is a slight scoliosis, with convexity to the left in the midthoracic region.

it was noted that the thorax was normally formed and symmetric but that there was a respiratory lag on the right side. The spinal column was straight. The trachea appeared to be deviated to the right of the midline. Percussion demonstrated dulness throughout the right hemithorax. No adventitious sounds were heard except an occasional tracheal gurgle. The point of maximum intensity of the heart beat was at the right nipple. The heart sounds were regular.

The electrocardiogram showed negative P waves and high diphasic deflections of the QRS complex, changes considered compatible with displacement of the heart. On roentgenographic

10. Münchmeyer: Zwei Beobachtungen von angeborenem Mangel der linken Lunge, Deutsche med. Wchnschr. **11**:295, 1885.

11. (*a*) Gilkey, H. M.: Congenital Absence of Lung, J. Missouri M. A. **25**:296, 1928. (*b*) de Toni, C.: Sopra un caso di agenesia del polmone destro con destrocardia, Clin. pediat. **16**:241, 1934.

examination, Dr. John R. Carty found the cardiac silhouette and the mediastinal contents in the right side of the chest continuous with the shadow of the liver. No iodized poppyseed oil entered the right bronchus. Bronchoscopy by Dr. John D. Kernan demonstrated that there was no carina and no right main bronchus.

On admission there were no signs of acute infection, but later there was inflammation of the left tympanic membrane and the temperature rose to 38.6 C. (101.8 F.) and later to 39.2 C. (102.6 F). Sulfadiazine was given. The pharynx became filled with mucus, and acute respiratory obstruction seemed imminent. A tracheotomy was performed, but she died when 2 months old.

At necropsy, there was no fluid in the peritoneum and the domes of the diaphragm were at the normal level. The left side of the thorax contained a large pleural cavity and lung. The cavity contained no fluid, and there were no adhesions. There was no recognizable

Fig. 2.—Heart and enlarged left lung from behind.

right pleural cavity. The pericardium extended almost to the right thoracic wall, from which it was separated only by a few fibrous strands. The larynx was well formed and normally located; the thyroid gland also was not remarkable. The thymus was moderately large and weighed 15.5 Gm. It did not appear to have obstructed respiration. The trachea formed an almost direct line with the left bronchus, with fifteen cartilaginous rings in the former and two in the latter. There was a barely recognizable pocket, not over 4 mm. in any dimension, at the normal site of branching of the right main bronchus. There was no tissue of any sort attached to the external aspect of the bronchus at this point. The heart was moderately large, but the chambers and valves were normal. The left border of the heart lay to the right of the midsternal line. The vascular connections of the heart and lung were normal except for a patent ductus arteriosus, complete absence of a right pulmonary artery and presence of only a small vein with the connections of a right pulmonary vein. The vagus nerves were not studied. The left lung was large. There was a shallow supernumerary sulcus on the anterior surface of its upper lobe. It was aerated except for small foci of

atelectasis and small foci containing polymorphonuclear leukocytes when examined microscopically. The liver showed fatty degeneration. All other organs and the diaphragm were normal in shape and appearance.

Death was attributed to bronchopneumonia and tracheal obstruction by mucus.

COMMENT

Agenesis of a lung is compatible with life. It has been reported in several soldiers and in 2 patients past 64 years old. However, pneumonia of the remaining lung is often fatal.[12] This factor seems to have been important in our case. There is even more direct danger from insufflation of a foreign body, the remaining bronchus having been occluded in 3 young children by a peanut and chewing gum[13] or by a peanut.[14]

It is of diagnostic importance that the chest in patients with true aplasia of a lung is usually symmetric. Only in the case of a man 49 years old described by Levy[15] was there significant asymmetry of the thorax. The retraction of the thorax so characteristic of secondary atrophy of a lung is significantly absent in agenesis.[11a] The preservation of symmetry is usually due to the enlargement, probably a true hypertrophy, of the remaining lung.

In 4 adults, fluid was present in the side of the thorax without a lung, and in 1 child a conspicuously enlarged thymus practically filled the space normally occupied by the lung. In many cases the pericardium and heart were adjacent to the thorax on the side of the absent lung, as in our patient.

Absence of the pleural cavity frequently accompanies absence of a lung, but a part of the contralateral lung may be found in the otherwise empty pleural cavity. We demonstrated no right pleural cavity. Absence of the pulmonary artery, veins and vagus nerve normally supplying the absent lung is the rule.[9] Abnormality of lobulation of the remaining lung with either fewer or more numerous sulci than normal has been noted at least 6 times and was present in our case. A number of minor variations in form of the trachea have been observed. Extrathoracic anomalies are comparatively rare when one lung is absent, but Bohnholtzer[16] reported the case of an infant with absence of the right lung and bronchi, ventricular septal defect, horseshoe kidney, undifferentiated sex organs and atresia of the urogenital tract and the anus. Killingsworth and Hibbs[17] found absence of the right lung associated with absence of the left kidney and ureter and one ovary and salpinx. Others have described exencephaly[18] and absence of a radius.[11a] On the other hand, multiple anomalies are the rule when both lungs are absent.[19]

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12. Jarisch, A.: Fehlen einer Lunge bei einem Frontsoldaten, Wien. klin. Wchnschr. **32**:736, 1919.

13. Goehle, O. L.: Foreign Body in the Bronchus of a Child with Congenital Absence of the Other Lung, Am. J. Dis. Child. **35**:733 (April) 1928. Mitchell, H. E.: Unusual Case of Foreign Bodies in the Food and Air Passages, Ohio State M. J. **32**:950, 1936.

14. Finner, L. L.: Congenital Absence of One Lung: Report of a Case with Autopsy, Clifton M. Bull. **18**:35, 1932.

15. Levy, C. S.: Congenital Absence of One Lung, Am. J. M. Sc. **159**:237, 1920.

16. Bohnholtzer, E.: Beitrag zur Kenntnis einseitiger Lungenagenesien, Beitr. z. path. Anat. u. z. allg. Path. **101**:614, 1938.

17. Killingsworth, W. P., and Hibbs, W. G.: Agenesis of the Lung: Review of the Literature and Report of a Case, Am. J. Dis. Child. **58**:571 (Sept.) 1939.

18. Minne, J., and Gernez, L.: Agénésie complète du poumon gauche chez un nouveau-né exencéphale, Ann. d'anat. path. **10**:503, 1933.

19. Meckel, J. F.: Manual of Descriptive and Pathological Anatomy, translated by A. S. Doane, Philadelphia, Carey & Lea, 1832. Schmit.[2]

In a few cases the form of the bronchial tree of the remaining lung has raised the possibility that it is the morphologic equivalent of two lungs.[20] However, the variability of bronchial branching described by Narath (cited by Müller [5]) renders this possibility unlikely.

The cause of agenesis is obscure. Müller [5] expressed the belief that it is unlikely that the absence of a lung is due to external pressure. It is much more probable that the agenesis is a primary defect of development, the enlargement of the other lung and absence of the homolateral vessels being secondary. Most authors [21] have expressed the opinion that the agenesis of the lung antedates absence of pulmonary vessels. Ellis,[1] however, postulated that the vascular anomalies precede and cause the absence of the lung.

An interesting indication that maldevelopment of the lung is a true developmental defect was furnished by Finkelstein (cited by Müller [5]), who described a pair of uniovular female twins that lived one week. At autopsy, one had a rudimentary left lung and an enlarged right lung; the other, a rudimentary right lung and an enlarged left lung.

SUMMARY

A case of complete absence of the right lung found in an infant 2 months old is reported. The diagnosis was made during life by physical, roentgenographic and bronchoscopic examination. It was confirmed at autopsy. The child died of pneumonia.

1300 York Avenue.

525 East Sixty-Eighth Street.

20. (*a*) Welsch, K.: Ein Fall von Mangel der rechten Lunge, Frankfurt. Ztschr. f. Path. **36**:192, 1928. (*b*) Minne and Gernez.[18]

21. Gross, W.: Ein Fall von Agenesie der linken Lunge, Beitr. z. path. Anat. u. z. allg. Path. **37**:487, 1905. Hart, C., and Mayer, E., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, pp. 468-469. Welsch.[20a] Müller.[5]

OMPHALOCELE WITH CONGENITAL OBSTRUCTION

REPORT OF A CASE WITH MECKEL'S DIVERTICULUM

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AND
R. L. NEVILLE, M.D.
SAVANNAH, GA.

Omphalocele, or exocelom, is a true congenital umbilical hernia containing intestine or abdominal organs. This condition is said to occur once in 5,000 to 6,000 newborn infants.[1] The presence of Meckel's diverticulum in an omphalocele has been reported only twice in the English literature.[2]

In the present case the intestines could not be reduced until the infant was anesthetized. One of us (H. J. M.) observed the size of the omphalocele increase from that of a lemon (approximately 6 cm. in diameter) to that of a medium-sized grapefruit (approximately 12 cm. in diameter) within five minutes after birth. This occurred through the swallowing of air when the infant began to cry. The intestines became distended, and this hindered any reduction. This was a most interesting physiologic observation. The infant was operated on when 80 minutes of age. Convalescence was uneventful, and at the age of 14 weeks she weighed 12 pounds 11 ounces (5,755 Gm.) and appeared perfectly normal.

REPORT OF CASE

Infant Annette C., the product of an eighth pregnancy, was born at 10:40 a. m. on Feb. 28, 1942. Respiration was spontaneous. There was an omphalocele present that measured 6 cm. in diameter; but as the infant cried and the intestines became distended with swallowed air, the size of the omphalocele increased to 12 cm. in diameter. Examination of the infant ten minutes after birth revealed no other congenital deformity. Preparation was made for immediate operation, which was begun at 12 midday and completed at 12:40 p. m.

Family History.—The mother and father were living and well. The mother's pregnancy and labor were normal, as were all other pregnancies except the fourth, which terminated at the end of two months in a miscarriage. Three brothers, aged 18, 14 and 12 years, were living and in good health. Three sisters, aged 10, 5 and 3 years, also were living and in good health.

Description of Operation.—The omphalocele was approximately 12 cm. in diameter; the wall of the sac was transparent, and through it, loops of intestine could be seen. An attempt was made to reduce the hernia, but this could not be done until the infant was anesthetized with ether. When the infant was relaxed, the operative field was prepared with green soap and water, alcohol, ether and tincture of merthiolate. The omphalocele was reduced with difficulty, reduction being maintained by a piece of sterile gauze held over the umbilical ring.

A longitudinal incision in the median line was made that extended approximately 2 inches (5 cm.) above and below the umbilicus, the base of the omphalocele being surrounded by an elliptic deviation of the incision just sufficient to embrace its neck. The incision was carried through the subcutaneous tissue and aponeurosis, exposing the parietal peritoneum; this was then carefully opened and the portion connected directly with the cord removed. The umbilical vessels were ligated with 0 chromic catgut.

At this point Meckel's diverticulum was noted. It was about 8 cm. in length and 5 cm. at its widest diameter and connected at its apex to the basal end of the vitellointestinal duct.

From the Pediatric Service, Telfair Hospital.

1. Thunig, L. A.: Hernia into Umbilical Cord and Related Anomalies, Arch. Surg. **33**:1021-1045 (Dec.) 1936.

2. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941. Mason, G.: A Note on the Association of Meckel's Diverticulum with Hernia, Newcastle M. J. **13**:73-81 (April) 1933.

Fig. 1.—A recent photograph of the patient.

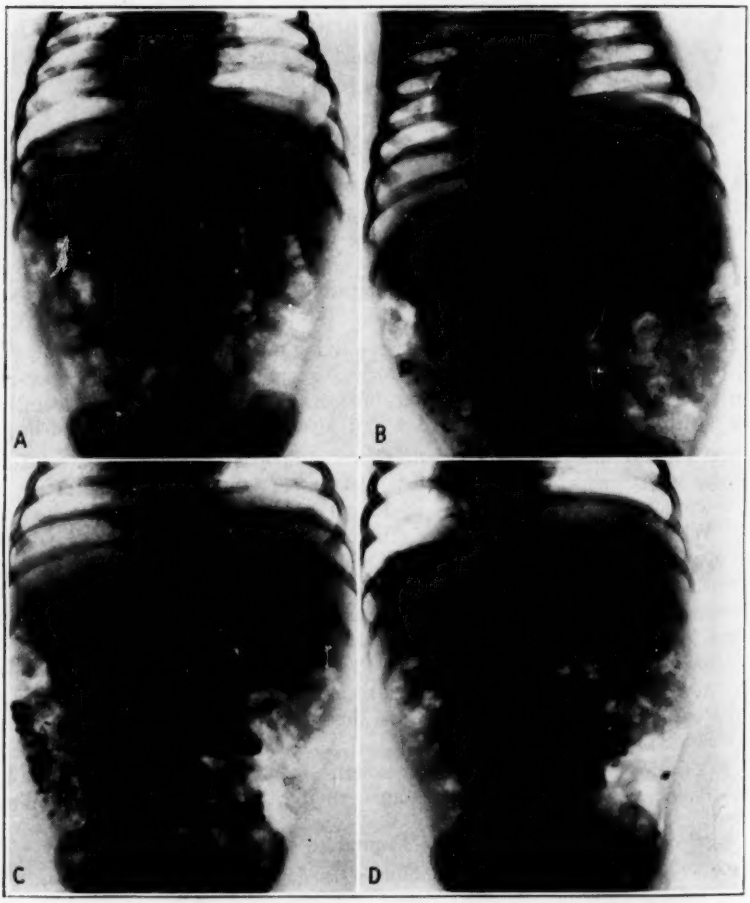

Fig. 2.—Roentgenograms made on July 9, 1942: *A*, before the ingestion of barium sulfate; *B*, immediately after the ingestion of barium sulfate; *C*, one hour, and *D*, two hours, after the ingestion of barium sulfate.

The base was ligated, and the umbilical vessels and the entire umbilical ring were removed. Then the stump of the vitellointestinal duct was inverted with a purse string suture of linen.

Further examination of the abdominal viscera was made, and other anomalies were not found. The wound was closed in layers. The peritoneum was closed with 00 chromic catgut. The edges of the rectus abdominis muscle, which had been previously exposed, were approximated with 00 chromic catgut. The fascia recta was closed with interrupted sutures of 0 chromic catgut and reenforced with interrupted sutures of silk. The subcutaneous tissue was approximated with interrupted sutures of plain catgut. The skin was closed with interrupted dermal sutures. Dressings were applied.

Postoperative Course.—The wound remained clean. The sutures were removed on the seventh day, and the patient made an uneventful recovery. Subsequent examinations showed the wound to be strong, with no sign of any ventral hernia.

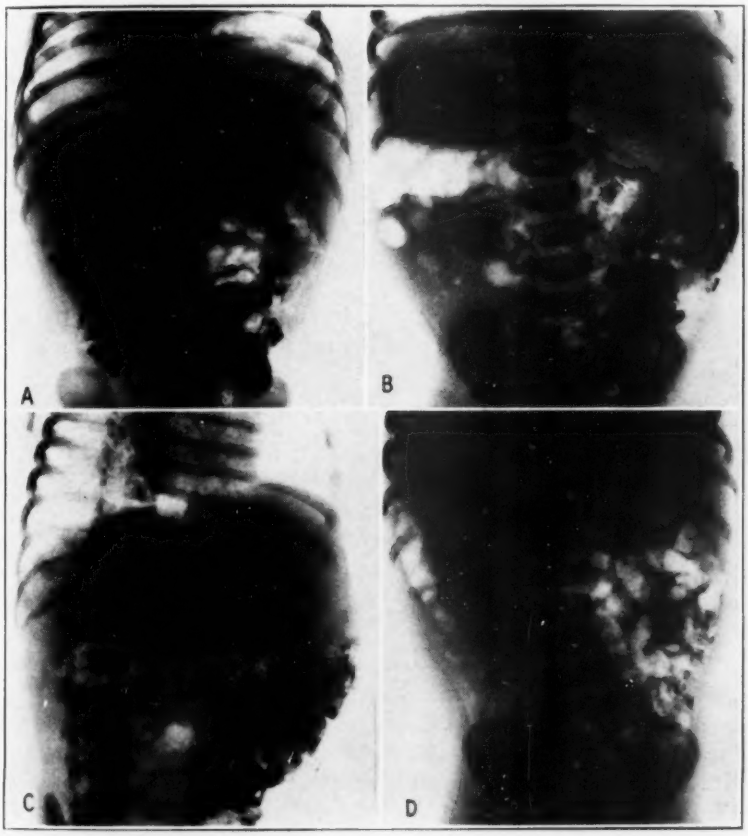

Fig. 3.—Roentgenograms made on July 9, 1942. *A*, three hours after the ingestion of barium sulfate; *B*, anteroposterior view, and *C*, oblique view, to show Meckel's diverticulum, four hours after the ingestion of barium sulfate; *D*, roentgenogram made on July 10, twenty-four hours after the ingestion of barium sulfate.

Postoperatively, oxygen was given ten minutes each hour for the first twenty-four hours. The infant was fed ¼ ounce (7.4 cc.) of a 5 per cent dextrose solution two hours after the operation. This was repeated every two hours for forty-eight hours, the amount being increased 1 drachm (3.7 cc.) at a time until 1 ounce (30 cc.) was given. After forty-eight hours, an evaporated milk, water and dextrimaltose formula was given—1 ounce (30 cc.) every three hours for three days. When the infant was 4 days old, she was put to the breast every four hours, with supplementary feedings of an evaporated milk formula. The feeding of orange juice was started at 3 weeks of age; of plain cod liver oil, at 6 weeks, and of cereal, at 3 months.

The child was examined on June 17 and weighed 12 pounds 11 ounces (5,755 Gm.). She was put on the following feeding schedule: evaporated milk, 13 ounces (383 cc.); water, 19 ounces (562 cc.); granulated sugar, 3 tablespoonfuls (45 Gm.), 8 ounces (237 cc.) being offered at 6 and 10 a. m., 2 and 6 p. m. and cereal being given at 10 a. m. and 6 p. m. Raw egg yolk was added to the cereal at 10 a. m. Two to 4 ounces (60 to 120 cc.) of orange juice and ½ teaspoonful (2 cc.) of cod liver oil were given daily.

On July 9, the results of a roentgen examination by Dr. Robert Drane were reported as follows:

"A preliminary roentgenogram shows nothing abnormal.

"After the oral ingestion of barium sulfate, films were made immediately and after one, two, three, four and twenty-four hours. There is a normal movement of the barium sulfate through the small and large intestines. There are no obstructing adhesions. The diverticulum cannot be visualized."

SUMMARY

A case of omphalocele with congenital obstruction is reported.

It is unusual for Meckel's diverticulum to be incorporated in the contents of the omphalocele.

The unusual physiologic phenomenon of the omphalocele's doubling in size when the infant began to cry was due to a valvelike obstruction, which caused air to distend the intestines within the omphalocele.

This infant was operated on at the age of 80 minutes.

The convalescence was uneventful, and the infant appeared perfectly normal at 14 weeks of age.

Roentgen examination at the age of 5 months failed to reveal the presence of Meckel's diverticulum. This is probably due to the fact that the diverticulum atrophied after the operation.

427 Bull Street.

11 West Gordon Street.

HEMANGIOMA OF THE ELBOW SUCCESSFULLY TREATED WITH RADIUM AT AN EARLY AGE

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As has been strongly emphasized by many therapeutists,[1] the earlier in life a hemangioma is treated, the more ready the response to irradiation, the better the cure and the smaller the ultimate disfigurement. There has been, however, a regrettable tendency among physicians as well as laymen to put off treatment of a birthmark of this type until later in life, in the mistaken belief that it may disappear of itself or, if it does not do so, that the child may later be better able to tolerate treatment. But experience has shown that, far from the child's outgrowing the lesion, hemangioma tends to grow along with normal development of the child. It is also a known fact that the younger the tissue the more sensitive it is to irradiation and therefore the earlier the treatment the easier to eradicate the lesion. There has also been a fear that if irradiation is administered to a very young child it may cause injuries to growing bones, especially when radium is applied at the area of a joint. All these reasons have little if any validity when treatment is properly and expertly given. The most serious of the objections is that of possible injury to growing bones, and it is this assumption I wish to correct.

It is, of course, true that there are recorded cases in which irradiation caused injury affecting growth of bone. Stevens [2] reported a case in which a shortened arm resulted from irradiation. Desjardins [3] also reported a case of maldevelopment of bone from irradiation, and others too have shown similar effects. A study of these reports, however, discloses that all of the injuries resulted from intensive purposely administered irradiation for a neoplasm.

Irradiation has been employed to correct asymmetry of the limbs, especially that due to poliomyelitis. Hinkle,[4] experimenting on animals, showed that the effect of irradiation on the epiphysis of one limb was to inhibit its growth, while the other limb grew normally. This observation was utilized in equalizing asymmetric limbs in cases reported by Judy and others [5] as well as by myself. However, this was a purposely intensive irradiation to a growing epiphysis. In the treatment of hemangiomas, on the other hand, only mild applications of small doses of radium are employed at long intervals repeated over an extended period of time and no intensive, persistent treatment is maintained over any one area. The effect is primarily on the vascular network forming the hemangioma. When properly administered, such radium emanations should be almost totally absorbed in the superficial tissues and should in no way affect the underlying growing bone.

1. Kaplan, I. I.: Urol. & Cutan. Rev. **44**:397-400 (June) 1940. Rosh, R.: Mississippi Valley M. J. **64**:43 (March) 1942. Pohle, E. A.: Am. J. Roentgenol. **41**:408-415 (March) 1940. Peterson, R., and Tod, M. C.: ibid. **42**:726-730 (Nov.) 1939.

2. Stevens, R. H.: Radiology **39**:39-47 (July) 1942.

3. Desjardins, A. U.: Radiology **14**:296-307 (March) 1930.

4. Hinkle, C. L.: Am. J. Roentgenol. **47**:439-455 (March) 1942.

5. Judy, W. S., and Spangler, D.: Am. J. Roentgenol. **46**:237-240 (Aug.) 1941; Radiology **37**:310-315 (Sept.) 1941.

Fig. 1.—Hemangioma on the elbow, before treatment.

Fig. 2.—The patient at 9 years of age. Note the equal development of the arms and the absence of discrepancy in length.

The proper technical application of radium is the important factor, and in twenty years of service at Bellevue Hospital I have never noted any untoward disturbance in bone.

I have the opportunity of reporting on a case in which treatment was applied directly over the elbow joint, opposite the epiphysis, where effects on the bone are most likely to be noted and in which the patient has been followed for nine years. The lesion is completely healed; there is no impairment of articular function, nor is there any evidence of involvement of bone, any impairment of epiphysial growth or any discrepancy in length of the bones of the treated arm when compared with the untreated limb.

REPORT OF A CASE

S. Z., a girl, was admitted to the radiation therapy service of Bellevue Hospital on July 13, 1933, at the age of 10 weeks. At birth a large, irregular, soft, compressible, reddish mottled tumor with the center ulcerated was noted over the outer and inner surfaces of the left elbow, directly over and forming part of the soft tissues of the elbow joint (fig. 1). Radium therapy was advised, and treatment was administered as follows:

On July 17, 24 and 31 and August 16 eight tubes containing 5 mg. of radium filtered with 1 mm. of platinum were applied over four layers of folded gauze for one hour at each sitting, that is, 40 milligram hours per sitting, to the lesion. Definite improvement was noted after the lapse of several weeks. No treatment was given again until September 11, when, because of residual growth, radium treatment was resumed and six tubes of 5 mg. each were applied for one hour, for a dose of 30 milligram hours. A definite reduction of the growth, healing of the ulcer and paling of the lesion were noted.

On September 25 two tubes of 15 mg. each filtered by 1½ mm. of platinum were applied directly to the superior and inferior edges of the lesion for one hour.

On October 10 the central ulcerated area was completely healed.

On October 25 some residual growth was still present and six tubes of 10 mg. each filtered with 1 mm. of platinum were applied on gauze over the lesion, placed about its periphery. A one hour treatment, for a dose of 60 milligram hours, was administered.

On November 20 another treatment was given to a persistent lesion along the lower edge. Four tubes of 15 mg. each filtered with 1.5 mm. of platinum were applied over gauze for one hour, or a dose of 60 milligram hours. This treatment was repeated on December 11, when eight tubes of 10 mg. each filtered through 1 mm. of platinum were applied for one hour, a dose of 80 milligram hours.

On Jan. 8, 1934 the edges of the lesion were still prominent, and treatment was given with one 25 mg. tube filtered with 1.5 mm. of platinum over the upper edge and three tubes of 15 mg. filtered with 1.5 mm. of platinum over the rim applied for thirty minutes, for a dose of 35 milligram hours.

On February 5 a small area of residual lesion was treated for 50 milligram hours with two tubes of 25 mg. each filtered with 1.5 mm. of platinum filter.

On February 19 and March 19 radium was applied to the edges of the lesion. Eight tubes of 10 mg. each filtered with 1 mm. of platinum were applied for one hour and one-half hour, for doses of 80 and 40 milligram hours respectively.

On June 18 six tubes of 10 mg. each filtered with 1 mm. of platinum filter were applied to the edges for one-half hour, for a dose of 30 milligram hours.

No further treatment was administered, but the patient was observed from time to time. In June 1942 the lesion was completely healed and the skin was soft and flexible. There was no shortening of the arm, and motion was excellent. Because of the supposition that radium might affect growing bone, roentgenograms were taken of the elbows on both sides and no evidence of deleterious effects was noted (fig. 2).

SUMMARY

Fear of adversely affecting growing bones in children with radium therapy is fallacious if irradiation is properly and expertly administered.

A case in which a hemangioma of the elbow was treated with radium is reported in detail. The patient has been followed over a period of nine years, from 10 weeks to 9 years of age.

755 Park Avenue.

Progress in Pediatrics

PEDIATRIC ASPECTS OF THE SALEM WITCHCRAFT TRAGEDY

A LESSON IN MENTAL HEALTH

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I

From the innermost recesses of his Puritan heart and soul, the Rev. Samuel Parris hated Sin. He hated all the Evil Angels, the Devil, Venomous Pilot of Hell; above all, he hated Shee-Witches and the whole Damned and Detestable Art of Witchcraft. Fate was indeed unkind to Parris, for when the terrible stench of witchcraft first became discernible in his little, secluded, backwoods parish of Salem Village, his own daughter Elizabeth and his niece Abigail were the very first to be afflicted. Though the real facts are rather obscure, according to all historical accounts it was actually Tituba, his West Indian servant girl, who initiated the events that culminated in the Salem tragedy, when, during some unexciting winter days and nights, she told weird tales and taught tricks of magic or sorcery to a group of imaginative girls who came to play in the Parris home. At any rate, in January 1692 some of these children became afflicted with a strange, unknown distemper. They crawled into holes, crept under benches and chairs, assumed "sundry odd Postures and [made] Antick Gestures, uttered foolish, ridiculous Speeches, which neither they themselves nor any others could make sense of." After many of the ministers from neighboring towns had met on a day of solemn fast and prayer and especially after Dr. Griggs, whose niece was also among the afflicted, had been unable to find any physical cause for this unusual behavior, it was decided that the children were certainly bewitched. In response to searching questions, the children alleged that they had been tormented by three women: Tituba, the servant; Goody Osburn, a sickly old creature who later in her trial admitted that she had suffered from vivid dreams, had heard voices and had not regularly attended church, and old Sarah Good, a pipe-smoking, disorderly and somewhat demented beggar. The trials got off to a dramatic start when Tituba confessed that she had often ridden through the air on a pole to witch meetings and that the very Devil himself, appearing before her sometimes as a black dog, a yellow bird or a red rat, had compelled her to torment the children on many occasions and in numerous ways. She also claimed that others were involved, and later, when some other women confessed that they too were pawns of the Devil, the witch hunt was on in earnest. At the preliminary hearings and subsequent trials, the children fell into extraordinary fits whenever Good or Osburn gazed on them. In witchcraft lore, it was a common belief that when a witch cast her evil eye on an innocent person some occult substance, called an "Apperishion," entered the body and mind of the victim but when the witch subsequently touched that person this substance was immediately released. On evidence of this sort, old Goody Osburn and Goody Good were promptly condemned to death.

An after-dinner talk at the annual meeting of the Society for Pediatric Research, Skytop, Pa., May 1, 1940.

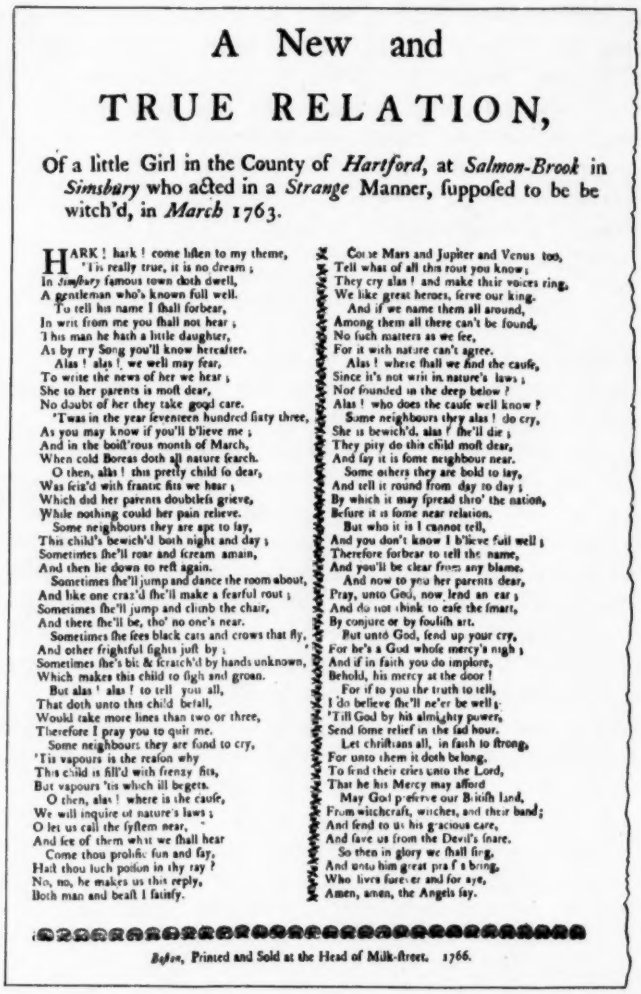
Panic rapidly spread throughout the neighboring countryside. Numerous others claiming to be afflicted heedlessly accused their imaginary tormentors until about 250 persons, mostly women, were arrested. The jails at Ipswich, Boston and Salem were packed beyond their capacities, and, though many escaped, two or three died in custody. Thirteen women and six men, many of them 60 to 80 years of age, were hanged, and one old man was slowly pressed to death with heavy stones for refusing to plead. Also among the victims were two dogs. The affair reached its climax when the afflicted persons began to accuse some of their prominent neighbors. A magistrate in Andover, after signing many warrants for the arrest of others, had to flee for his own life when he was accused of being an accomplice of the witches merely because he had refused to indict an obviously innocent person. The governor's wife and the wife of a minister who had been active in ferreting out witches were also incriminated. Finally, in May 1693, when the whole affair was obviously getting out of hand and was rapidly making itself ridiculous to thoughtful persons, the governor dissolved the special court and released all the suspects still in jail. According to a contemporary account: "The Lord then so chained up Satan, that the afflicted grew presently well."

II

Even while some of the "Fire Brands of Hell" were still dangling by their necks on Gallows Hill, the more conscientious of the bewildered spectators, suddenly realizing that something had gone awry, began to cry pitifully to Heaven for forgiveness; and soon thereafter the first of the numerous historians began to offer explanations or apologies for this horrible tragedy. This black page of American history certainly needed explanation, but the explanations are nearly as numerous as the historians themselves. In the volumes devoted to witchcraft in Salem appear some theories to explain how such a catastrophe could happen in this little colonial town of a few hundred God-fearing inhabitants. It has been shown that from the fourteenth to the seventeenth century there was a widespread belief in witchcraft throughout the Christian world, with the result that in Europe between 200,000 and 500,000 persons were burned at the stake or put to death in other ways for witchcraft. Though a few brave men had previously risked their fortunes and their very lives by denying the existence of "secret, black, and midnight hags," by 1692 the vast majority of persons here and abroad, including the greatest theologians, scientists, lawyers and physicians, indeed nearly every one except the "learned witlings of the Coffee House," sincerely believed that witches and their male counterparts, wizards, were made of real flesh and blood, could really evaporate into fog and filthy air and, being in league with the Devil, were always intent on harming ordinary mortals. Because this belief in witchcraft was so widespread, some attempt has been made to minimize the Salem tragedy as only a brief and transitory scene in a worldwide drama. But even though it is true that there were only about 30 victims of witchcraft in all the North American colonies and that the only horrible episode lasted little more than a year, in contrast to the centuries of persecution for witchcraft abroad, the Salem tragedy, nevertheless, still stands as one of the outstanding events of American history and still arouses curiosity, because it involved man's deepest emotions and had many aspects difficult to explain.

Though occasional cases of witchcraft cropped out in nearly all of the colonies during the last half of the seventeenth century, the reason it reached its climax in Massachusetts and not in Virginia, for instance, is usually attributed to the Puritan belief, as expressed by the Rev. Cotton Mather and the Rev. Samuel Parris, that a

real, personal, revengeful Devil, previously in full possession of the heathen Indians and their lands, was then concentrating his attention on New England in a brazen attempt to regain his lost possessions by the destruction of all churches and all religion. In short, the Kingdom of God in New England was in imminent jeopardy. From their reading of foreign books on witchcraft, the leaders of New England, many of them able, educated men, were well informed on how to detect and try a witch; and, since any alliance with the Devil was a heinous sin, they considered it



A New and

TRUE RELATION,

Of a little Girl in the County of *Hartford*, at *Salmon-Brook* in *Simsbury* who acted in a *Strange* Manner, ſuppoſed to be be witch'd, in *March* 1763.

HARK! hark! come liſten to my theme,
'Tis really true, it is no dream;
In *Simſbury* famous town doth dwell,
A gentleman who's known full well.
To tell his name I ſhall forbear,
In writ from me you ſhall not hear;
This man he hath a little daughter,
As by my Song you'll know hereafter.
Alas! alas! we well may fear,
To write the news of her we hear;
She to her parents is moſt dear,
No doubt of her they take good care.
'Twas in the year ſeventeen hundred ſixty three,
As you may know if you'll b'lieve me;
And in the boiſt'rous month of March,
When cold Boreas doth all nature ſearch.
O then, alas! this pretty child ſo dear,
Was ſeiz'd with frantic fits we hear;
Which did her parents doubtleſs grieve,
While nothing could her pain relieve.
Some neighbours they are apt to ſay,
This child's bewich'd both night and day;
Sometimes ſhe'll roar and ſcream amain,
And then lie down to reſt again.
Sometimes ſhe'll jump and dance the room about,
And like one craz'd ſhe'll make a fearful rout;
Sometimes ſhe'll jump and climb the chair,
And there ſhe'll be, tho' no one's near.
Sometimes ſhe ſees black cats and crows that fly,
And other frightful ſights juſt by;
Sometimes ſhe's bit & ſcratch'd by hands unknown,
Which makes this child to ſigh and groan.
But alas! alas! to tell you all,
That doth unto this child befall,
Would take more lines than two or three,
Therefore I pray you to quit me.
Some neighbours they are fond to cry,
'Tis vapours is the reaſon why
This child is fill'd with frenzy fits,
But vapours 'tis which ill begets.
O then, alas! where is the cauſe,
We will inquire of nature's laws;
O let us call the ſyſtem near,
And ſee of them what we ſhall hear
Come thou prolific ſun and ſay,
Haſt thou ſuch poiſon in thy ray?
No, no, he makes us this reply,
Both man and beaſt I ſatisfy.
Come Mars and Jupiter and Venus too,
Tell what of all this rout you know;
They cry alas! and make their voices ring,
We like great heroes, ſerve our king.
And if we name them all around,
Among them all there can't be found,
No ſuch matters as we ſee,
For it with nature can't agree.
Alas! where ſhall we find the cauſe,
Since it's not writ in nature's laws;
Nor founded in the deep below?
Alas! who does the cauſe well know?
Some neighbours they alas! do cry,
She is bewich'd, alas! ſhe'll die;
They pity do this child moſt dear,
And ſay it is ſome neighbour near.
Some others they are bold to ſay,
And tell it round from day to day;
By which it may ſpread thro' the nation,
Before it is ſome near relation.
But who it is I cannot tell,
And you don't know I b'lieve full well;
Therefore forbear to tell the name,
And you'll be clear from any blame.
And now to you her parents dear,
Pray, unto God, now lend an ear;
And do not think to eaſe the ſmart,
By conjure or by fooliſh art.
But unto God, ſend up your cry,
For he's a God whoſe mercy's nigh;
And if in faith you do implore,
Behold, his mercy at the door!
For if to you the truth to tell,
I do believe ſhe'll ne'er be well;
'Till God by his almighty power,
Send ſome relief in the ſad hour.
Let chriſtians all, in faith to ſtrong,
For unto them it doth belong,
To find their cries unto the Lord,
That he his Mercy may afford
May God preſerve our Britiſh land,
From witchcraft, witches, and their band;
And ſend to us his gracious care,
And ſave us from the Devil's ſnare.
So then in glory we ſhall ſing,
And unto him great praiſe bring,
Who lives forever and for aye,
Amen, amen, the Angels ſay.

Boſton, Printed and Sold at the Head of Milk-ſtreet. 1766.

Fig. 1.—A broadside of 1766 from Boston, dealing with a belated case of witchcraft. (Published by courtesy of the American Antiquarian Society.)

their first duty to caution their people to watch for any evidence of diabolic possession. It was no fairy tale that the wily and deceitful Devil would first attempt to get possession of human souls, even pious ones if possible; and, should he succeed, these contemptible, treacherous cohorts would, in turn, possess the power to torment other innocent persons in order to make them sign the Devil's book, willingly or no. All this may sound pretty foolish today, but it should be remembered, first of all, that the Puritans were in dead earnest, constantly striving to uplift the pitiful state of man even in the face of vehement criticism. Cotton

Mather clearly expressed it when he said: "Flashy people may burlesque these things, but . . . hundreds of the most sober people of a country, where they have as much mother-wit certainly as the rest of mankind, know them to be true. . . ."

So, when the Devil in a "vehement and terrible Rage" attempted to set up his own kingdom in or near Salem, which, after all, was the very birthplace of Puritanism in America, it was tantamount to a declaration of war—not an ordinary colonial war for the possession of lands against an ordinary enemy like the Indians or the French, but an intense, emotional religious war that was to determine, once and for all, whether righteousness, truth and honor should eternally prevail over injustice, wickedness and depravity. Emblazoned on the Puritan standard was the biblical injunction "Thou shalt not suffer a witch to live."

The more immediate causes of the "Witchcraft Delusion" have been frequently disputed by many able historians. It used to be customary to fasten all the blame on Cotton Mather, the most representative member of the clergy, for his misguided zeal in spreading all this so-called superstition and thereby indirectly causing all the subsequent trouble. This is not the place to discuss Mather's relation to the legal aspects of the trials, whether or not he influenced the governor to appoint a special court or the judges to admit the spectral testimony. Suffice it to say that Cotton Mather with his soul-terrifying sermons and pamphlets no doubt vigorously fanned the flame of witchcraft; but if he went off to war as the self-appointed "Ambassador of the Lord," it was only because he, like his father and grandfather before him, was one of the most respected leaders of the people and, having devoted nearly his whole life to the spreading of the Gospel in New England, he considered that to put down this "rebellion against the sovereignty of God" was not only his sacred privilege but his bounden duty. He was eminently sincere, and, besides, as I hope to show later in more detail, he himself had discovered some incontrovertible evidence of witchcraft.

But no one man could have possibly influenced a people to hang some of the most upright members of their church unless, deep in their emotional life, lurked something which might have prepared them to commit so horrible a blunder. I believe that fundamentally there existed a problem involving the mental health of the Puritan children. To show this it is necessary to reexamine some of the contemporary records; but, since it would be too tedious to discuss all aspects of the case, I propose to limit the discussion to those aspects which help to explain the peculiar behavior of the "afflicted children."

III

From a medical standpoint, the most interesting part of the witchcraft trials concerns the behavior and testimony of the girls. Of the ten, four were servants 17 to 20 years of age; one of them at least had apparently been frequently overworked and beaten, so doubtless had a reason to testify that her master was a wizard. As the trials progressed, more and more persons became "afflicted," until there were about 50 who claimed to be bewitched; but concerning most of these, particularly the young and middle-aged men and women, there is only meager information. Nor can much be said about Elizabeth Parris, the 9 year old daughter of the minister, for, although she is said to have been one of the chief accusers, she appeared in only one trial and had only a few fits. But among the ringleaders appeared the truly remarkable Ann Putnam, 12 years old, who testified in nineteen trials; the 11 year old niece of of the minister, Abigail Williams, who testified in eight trials, and Elizabeth Hubbard, 17 years old, who testified in twenty trials. Though there

were many adult witnesses in most of the trials, nearly all of the victims were condemned chiefly on the testimony and behavior of the girls.

As has been stated, the usually accepted version is that the children had been led astray by the weird tricks and stories of Tituba, the servant in the Parris home. There is a little doubt about this, however, for Robert Calef, who was one of the first to question the validity of the witchcraft trials and on whose writings a good deal of the Salem story depends, said that Tituba had been beaten by her master until she was very willing to confess that she had ridden through the air and had partaken of the Devil's sacraments. Nevertheless, the belief still persists, especially among popular authors, that the children began, innocently at first, to practice their magic tricks, which to them was only sport but which of course was intolerable under the roof of any good New England minister's home, and, having been caught, rather than suffer the punishment that was sure to befall them they began to act even more strangely and to pretend that their actions were far beyond their control. Once having ventured to name the actual witches who were tormenting them, they continued in their nefarious schemes regardless of consequences. In other words, it

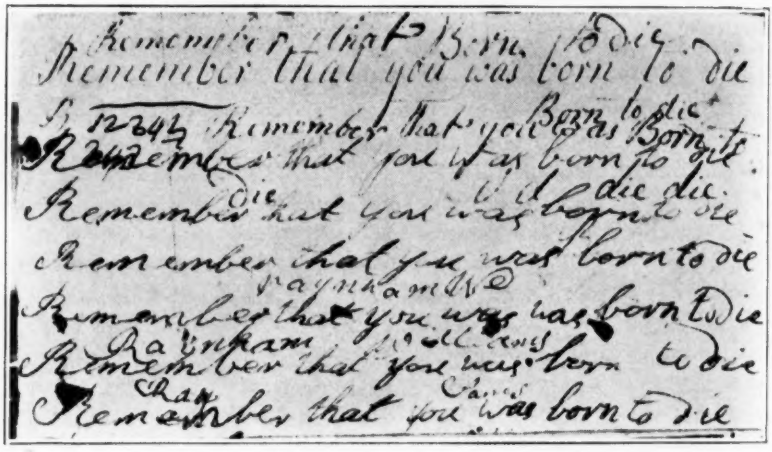


Fig. 2.—"Remember that you was born to die." A lesson in penmanship. (Reproduced from Edmund Williams' copy of Nathaniel Ames's "Astronomical Diary or an Almanack for 1753" and published by permission of the American Antiquarian Society.)

is the common belief that they were exceedingly bad, dishonest children who did not realize the seriousness of their tricks or games, who derived considerable personal gratification from being the center of the excitement or were, perhaps from spite, deliberately deceitful from the very beginning and continued so in all their acts and testimony.

The array of historians who have thought that the children were primarily to blame for the whole witchcraft imbroglio is a notable one. Calef, writing in 1697, was among the first to express suspicion of the motives of the children, when he pointed out that in one of the trials they complained of being bitten and displayed the bites on their arms even when the accused "had not a tooth in his head wherewith to bite." Hutchinson, an early historian who talked with many of the courtroom spectators, thought that the judges and jury were altogether too credulous in believing such "fraud and imposture" on the part of the children. Upham, the most thorough of the witchcraft students, devoted almost the whole of his two volumes to proving his discovery of a horrible conspiracy on the part of Parris and particularly of the children, who with fiendlike satisfaction descended to the very

depths of wickedness and depravity in their testimony, which was nothing short of "wicked perjury and wilful malice." Professor Kittredge mentioned the children's "pranks." Even in the last few years the popular Kenneth Roberts, in his "Trending into Maine" (1938), described the witchcraft children as "a group of the coldest blooded and most malignant brats ever spawned," and the entertaining Eleanor Early, in her "New England Sampler" (1940), took particular delight in referring to them as "The Puritan Song and Dance Girls . . . eight of the nastiest brats on record." Nothing is to be gained by citing numerous other authorities who have accepted this interpretation; it should be mentioned, though, that a few of them have asserted flatly that the whole sorrowful performance could easily have been averted by a good stiff birch rod frequently and liberally applied.

The basis for this harsh opinion of the children is that they frequently told the most deliberate lies. They actually seemed eager to testify against any poor old crone brought into court, saying that they had been long tormented by the accused, when it was plainly apparent that they had never seen or heard of the supposed witch until that very day. They would swear with the utmost sincerity that they had seen the defendant at a witch assembly on a particular day when, as even the judges and jury must have known, the accused was in another town or chained in jail. They told the most fantastic atrocity stories of what happened at those meetings but asserted that not by tempting promises, horrible tortures or even threats of death had they been made to jeopardize their own little innocent souls by signing the Devil's book. With gory details they excitedly related the confessions to murders which they claimed to have extracted from the defendants or their "apparitions" and thus explained many deaths in the neighborhood which up to that time had been most mysterious.

There were many other peculiar complaints not altogether unrelated to their lies. Nearly all of the children swore repeatedly that they had been pinched, choked and bitten, occasionally exhibiting marks of the bites or pinches on their arms. Screaming hideously, they would claim that pins and knives were being stuck into their bodies. There were times when many apparently could not talk or walk; some appeared suddenly struck deaf, dumb and blind all at once. Others complained of a mist before their eyes or of stomach sickness or of breathlessness. Over and over again the "apparitions" appeared to them, sometimes as a yellow bird, a cat with ears like a man, a little turtle, a streaked snake or a hairless pig. The Devil appeared to Susannah Sheldon on at least three different occasions and always in the form of a little black man in a high-crowned hat.

Regardless of what the children said, the evidence most convincing to the judges, jury and spectators came when the judges ordered the afflicted children to look on the captured witches, whereupon they promptly went off into fits but, as a general rule, recovered as soon as the accused were made to touch them. This sort of evidence appears with monotonous regularity throughout the court records, and the apparent ease with which the children threw and recovered from their fits has been considered absolute proof that they were merely acting. The more one reads between the lines, however, the more it becomes evident that it was generally those "hideous clamours and screechings" that made their stories seem true, and it is also apparent that the dramatic and "violent fits of torture" were ample proof to nearly all who saw them that the children were actually bewitched. Herein lies the crux of the whole Salem episode. Whether or not to blame the children for the executions depends almost entirely on the true nature of the fits; and it is a curious fact in the history of witchcraft in New England that the judges, jury and spectators who actually saw those fits had not the slightest doubt that the children were being

tormented, while most the historians, who based their conclusions on the cold, disconnected and imperfect transcriptions of the court records, believed that the children were only putting on a show. Unfortunately, in the Salem records the fits are not described in any connected fashion, and one has to piece together many stray bits of testimony to get a clear conception of their nature; yet so palpably convincing was this evidence of bewitchment that the help of 12 year old Ann Putnam and her friends was sometimes sought by persons in distant towns when they suspected witchcraft in their households. In one instance, a man brought his sick infant from Boston to Salem merely for these girls to name the persons who had bewitched his child and two women of Boston were actually named, though the girls had never seen them. At another time, the afflicted Ann, so richly endowed with extrasensory perception, was taken to Andover to see a sick old woman, and before long fifty of the inhabitants of that town were under arrest for witchcraft. The conclusion seems inescapable that if these children were merely putting on a show they displayed consummate skill in acting in an extraordinary show indeed.

IV

Fortunately, because it is helpful in the diagnosis, there still exists a record of one case of witchcraft in which the fits of some bewitched children are described in great detail. This is called "Memorable Providences, Relating to Witchcraft and Possessions," and chiefly because of its detailed descriptions it is a most valuable contribution to early American medicine, though not hitherto so regarded. This case history of the Goodwin children was written a few years before the Salem tragedy. On the surface, it may seem illogical to use a Boston witchcraft case of 1688 to help explain the Salem cases of 1692, but all historians agree on the almost perfect similarity [1] in the cases and my only reason for citing these earlier cases from Boston is that here one finds a connected story limited almost exclusively to a description of the fits. Another objection to using the "Memorable Providences" is that the author, Cotton Mather, is known to have been prejudiced in favor of witchcraft. But strange as it may seem to some, the Puritans, and particularly Cotton Mather, did not oppose, but indeed advanced, the growth of science. It was this same Cotton Mather, member of the Royal Society, who wrote the first American description of measles (which, incidentally, is an American classic), and it was he who, in spite of tremendous opposition from the medical profession, influenced Zabdiel Boylston to try inoculation against smallpox, the first step toward the prevention of diseases. Mather steadfastly maintained in his "Memorable Providences" that he was recording actual facts, and, though considerable allowance should be made for his superstition, gullibility and firm belief in witchcraft, it is clear that the descriptions must have been founded mostly on observations, not only because of the similarity to the Salem court records, with which he had nothing to do, but chiefly because, even after these two hundred and fifty years, one can recognize the sickness that afflicted the Goodwin children as easily as though they had had the smallpox.

1. This similarity is so striking that any explanation of Salem witchcraft should be applicable to the Goodwin cases. This automatically eliminates the role of Tituba, the Salem Village jealousies and dissensions, the mob hysteria in the Salem courtroom and numerous other theories of students of witchcraft. These students generally dismiss the Goodwin cases on the supposition that the children of Salem had read Mather's account and had decided to imitate the Goodwin children. Totally ignored is the more plausible theory that the adults of Salem Village had read Mather's account and were thus able to recognize witchcraft when they saw it.

The "Memorable Providences" concerns John Goodwin, a mason, and his wife, who with their six children, Nathaniel 15, Martha 13, John 11, Mercy 7 and Benjamin 5 years and Hannah 6 months old, comprised an extremely religious family. Indeed, from some of his devout letters still extant it appears that John Goodwin was the kind of mason who would have said a prayer every time he laid a brick. One day Martha Goodwin accused the family washerwoman of stealing some of the family linen, whereupon the washerwoman's "wild Irish" mother, old Goody Glover, "bestow'd very bad Language upon the Girl . . . immediately upon which, the poor child became variously indisposed in her health, and visited with strange Fits, beyond those that attend an Epilepsy, or a Catalepsy, or those they call The Diseases of Astonishment." Shortly after, John, Mercy and Benjamin began to behave in a strange manner too, though "the godly father and the suckling Infant, were not afflicted" nor was Nathaniel except in slight degree. The most skilful Boston physicians, unable to find any physical cause, concluded that the children were afflicted with "an Hellish Witchcraft," and, needless to say, poor Goody Glover was therefore put to death. Later, Cotton Mather took the afflicted Martha Goodwin into his own home and after many months of observation wrote his account, from which the following passage is taken:

The variety of their tortures increased continually; and tho about Nine or Ten at Night they alwaies had a Release from their miseries, and ate, and slept all night for the most part indifferently well, yet in the day time they were handled with so many sorts of Ails, that it would require of us almost as much time to Relate them all, as it did of them to Endure them. Sometimes they would be Deaf, sometimes Dumb, and sometimes Blind, and often, all this at once. One while their Tongues would be drawn down their Throats; another-while they would be pull'd out upon their Chins, to a prodigious length. They would have their Mouths opened unto such a Wideness, that their Jaws went out of joint; and anon they would clap together again with the Force like that of a strong Spring-Lock. The same would happen to their Shoulder-Blades, and their Elbows, and Hand-wrists, and several of their joints. They would at times ly in a benummed condition; and be drawn together as those that are ty'd Neck and Heels; and presently be stretched out, yea, drawn Backwards, to such a degree that it was fear'd the very skin of their Bellies would have crack'd. They would make most pitteous out-cries, that they were cut with Knives, and struck with Blows that they could not bear. Their necks would be broken, so that their Neck-bone would seem dissolved unto them that felt after it; and yet on the sudden, it would become again so stiff that there was no stirring of their Heads; yea, their Heads would be twisted almost round; and if main force at any time obstructed a dangerous motion which they seem'd to be upon, they would roar exceedingly . . .

The Fits of the Children yet more arriv'd unto such Motions as were beyond the Efficacy of any natural Distemper in the World. They would bark at one another like Dogs, and again purr like so many Cats. They would sometimes complain, that they were in a Red-hot Oven, sweating and panting at the same time unreasonably: Anon they would say, Cold water was thrown upon them, at which they would shiver very much. They would cry out of dismal Blowes with great Cudgels laid upon them; and tho' we saw no cudgels nor blowes, yet we could see the Marks left by them in Red Streaks upon their bodies afterward. And one of them [John, 11 years old] would be roasted on an invisible Spit, run into his Mouth, and out at his Foot, he lying, and rolling, and groaning as if it had been so in the most sensible manner in the world; and then he would shriek, that Knives were cutting of him. Sometimes also he would have his head so forcibly, tho not visibly, nail'd unto the Floor, that it was as much as a strong man could do to pull it up. One while they would all be so limber, that it was judg'd every Bone of them could be bent. Another while they would be so stiff, that not a joint of them could be stir'd. . . .

Many wayes did the Devils take to make the children do mischief both to themselves and others; but thro the singular Providence of God, they always fail'd in the attempts. For they could never essay the doing of any harm, unless there were some-body at hand that might prevent it; and seldome without first shrieking out, "They say, I must do such a thing!" Diverse times they went to strike furious Blowes at their tenderest and dearest friends, or to fling them down staires when they had them at the top, but the warnings from the mouths of the children themselves, would still anticipate what the Devils did intend. They diverse times were very near Burning or Drowning of themselves, but the Children themselves by their

own pittiful and seasonable cries for help, still procured their Deliverance. . . . But if any small Mischief happen'd to be done where they were; as the Tearing or Dirtying of a Garment, the Falling of a Cup, the breaking of a Glass or the like; they would rejoice extremely, and fall into a pleasure and Laughter very extraordinary . . .

Variety of Tortures now seiz'd upon the Girl [Martha, 13 years old]; in which besides the forementioned Ails returning upon her, she often would cough up a Ball as big as a small Egg, into the side of her Wind-pipe, that would near choak her, till by Stroking and by Drinking it was carried down again . . .

The Last Fit that the young woman had, was very peculiar. The Dæmons having once again seiz'd her, they made her pretend to be Dying, and Dying truly we fear'd at last she was: She lay, she tossed, she pull'd just like one Dying, and urged hard for some to dy with her, seeming loth to dy alone. She argued concerning Death, in strains that quite amazed us; and concluded, That though she was loth to dy, yet if God said she must, she must; adding something about the state of the Country, which we wondered at. Anon, the Fit went over; and as I guessed it would be, it was the last Fit she had at our House.

V

Inasmuch as old men and women were condemned to death as wizards and witches on this sort of evidence, it is easy to understand the unbridled scorn of the historians; and yet it is important to emphasize that there is enough here, to say nothing of other passages not cited, for an absolute diagnosis. It is also easy to show that the Salem children suffered from hysteria too, for there is hardly a sign or symptom manifested by Martha Goodwin that did not have its counterpart in one or another of the Salem children during their bewitchment. They too made "great noises" during their "lamentable fits and agonies"; they too were "dreadfully tortured" and "struck dumb and senseless for a season"; according to the Rev. Mr. Hale, "Sometimes they were taken dumb, their mouths stopped, their throats choked, their limbs wracked and tormented so as might move an heart of stone." Samuel Sewall, of all the Puritans the most generally successful in keeping his feet on the ground, meant exactly what he said when he wrote in his diary: "It was awful to see the tortures of the afflicted." During the trial of that "rampant hag" Martha Carrier, the afflicted were "so tortured that every one expected their death upon the very spot."

By patching together the sworn testimony of numerous witnesses during the trial of Mary Easty and by making a few minor alterations for the sake of continuity, one can obtain a fairly connected first-hand description of the fits of the Salem children on one occasion at least. At the preliminary hearing in Salem Village during April 1692, five of the afflicted children were "choked in such a most grievous maner" that the examination had to be interrupted, and in spite of the prayers of the Rev. Mr. Hale they remained "almost choked to death." For some now unknown reason Mary Easty was released on May 18. On May 20, Mercy Lewis, a 17 year old servant girl, had a fit in the home of her master, Constable John Putnam.

One man testified:

I went to that house about 9 a clock in the morning and when I came there Mercy Lewis lay on the bed in a sad condition and continued speechless for about an hour. [He then left for a while but came back.] She continued in a sad condition the greatest part of the day being in such tortures as no tongue can express; but not able to speak. But at last she said "Deare Lord Receive my soule" and again said "Lord let them not kill me yett" but at last she came to herself for a little while and was very sensible and then she said that Goody Easty said she would kill her before midnight. . . . Then again presently she felt very bad and cried out "Pray for the salvation of my soule for they will kill me."

Four other men who were in that house between 8 and 11 o'clock that night testified that Elizabeth Hubbard, another 17 year old girl, was brought in while they were there. They found Mercy Lewis "in such a case as if death would have

quickly followed . . . being unable to speak most of the day." The two girls then "fell into fits by turns, the one being well whilst the other was ill . . . and [the apparition] vexed and tortured them both by choking and seemingly breathless fits and other fits, threatening Mercy Lewis with a winding sheet & afterwards with a Coffin if said Mercy would not signe the Devil's book. Abundance more of vexations they both received from her [the apparition]."

Still two other men had been at the house that day and found Mercy Lewis

> in a very Dreadful and Solemn Condition so that Shee could not continue long in this world without a mitigation of those Torments. [They left the house for a while but] Returning the same night aboute midnight, wee found Mercy Lewis in a Dreadful fitt but her reason then Returned Again. She said "What, have you brought me the winding sheet, Goody Easty? Well, I had rather go into the winding sheet than Sett my hand to the Devil's book" but after that her fitts was weaker and weaker but still complaining that Shee was very sick of her stomake. About break of Day She fell asleep but still Continues extreem sick and was taken with a Dreadful fitt just as we left her so that we perceived life in her and that was all.

Another man testified that she was "grievously afflicted and tortured . . . choked allmost to death . . . and we looked for nothing else but present death." Her fit continued well into the next day.

During most of the fit the girl was in a stupor and could not speak; so Ann Putnam (12 years), Abigail Williams (11 years) and Elizabeth Hubbard (17 years) were summoned to the bedside to attempt to identify the apparition that was tormenting Mercy Lewis. The three said that it was the apparition of Goody Easty. Near midnight, when the fit was extra severe, two men rushed out of that haunted house, hastened to Salem for a warrant and then went to Topsfield and dragged Goody Easty out of bed. She was 58 years old and the mother of seven children, yet they took her back to Salem jail and chained her in a cell. She was brought to trial, and, chiefly because of Mercy Lewis' fit and similar evidence, she was convicted and subsequently hanged.

Because of the similarity in the two instances, one could expect that the same historians who have considered the Salem children as "frauds" should have also condemned the Goodwin children as deceitful "pests," they apparently having overlooked the fact that Cotton Mather, like the Salem judges, did consider the possibility of sham but quickly rejected it. Just because some passages in the "Memorable Providences" make it appear as though Martha Goodwin may have had her tongue in her cheek while she was being observed, one can hardly conclude that Cotton Mather's whole account was ludicrous, written in a "style of blind and absurd credulity that cannot be surpassed." That the children's afflictions were attributed to the capital crime of witchcraft is deplorable enough, to say the least, but that is not the point at issue. It is essential to remember that lying was only a symptom and that primarily the children were afflicted with a mental illness. Having studied medicine and probably knowing as much about sickness as any New England physician, Mather deserves a little credit for recognizing that there was at least something unusual about this girl. "But I am resolved after this" he wrote after observing her for many months, "never to use but one grain of patience with any man that shall go to impose upon me a Denial of Devils, or of Witches. I shall count that man Ignorant who shall suspect, but I shall count him down-right Impudent, if he Assert the Non-Existence of things *which we have had such palpable convictions of.*" (The italics are mine).

It therefore seems reasonable to conclude that not the apparent lying but the "extreme agony of all the afflicted" accounts for the decided convictions of the judges, jury and spectators, many of them educated and reasonable men. In some

cases "the tortures and lamentations of the afflicted" convinced even the relatives of the accused, and in the trials of Rebecca Nurse and a few others even the accused themselves, though vehemently denying their own guilt, nevertheless admitted that the children acted as though bewitched. Not unimportant is the fact that more than one trial had to be postponed because the children could not possibly be relieved of their "agony" by binding the accused, by prayer or by any other means. And when their trials were over, at least two convicted witches were unanimously excommunicated from the church, a horrible punishment in Puritan times, especially to one about to die. The possibility that the judges were unfair being laid aside for the moment, would the men and women of the church willingly and unanimously convict their intimate friends, whom they knew to be otherwise honorable, except for this very, very convincing evidence of "stupendous Witchcraft?"

VI

Far more fundamental to a true understanding of the Salem tragedy than the diagnosis of hysteria are the factors at play which could have caused so much hysteria among the children of those days; hence, by far the most interesting feature of Mather's account of the Goodwin children is that every now and then he allows a glimpse of the underlying cause. The following quotation is not an isolated passage lifted from its context merely to prove a point but is representative of many similar passages, and consequently the cause and effect sequence seems more than accidental:

But nothing in the World would so discompose them as a Religious Exercise. If there were any Discourse of God, or Christ, or any of the things which are not seen and are eternal, they would be cast into intolerable Anguishes. Once, those two Worthy Ministers, Mr. Fisk and Mr. Thatcher, bestowing some gracious Counsils on the Boy, whom they then found at a Neighbours house, he immediately lost his Hearing, so that he heard not one word, but just the last word of all they said. Much more, All Praying to God, and Reading of his Word, would occasion a very terrible Vexation to them: They would then stop their own Ears with their own Hands; and roar, and shriek; and holla, to drown the Voice of Devotion. Yea, if any one in the Room took up a Bible to look into it, tho the Children could see nothing of it, as being in a croud of Spectators, or having their Faces another way, yet would they be in wonderful Miseries, till the Bible were laid aside. In short, No good thing must be endured near those Children, which (while they are themselves) do love every good thing in a measure that proclaims in them the Fear of God. . . .

Devotion was now, as formerly, the terriblest of all the provocations that could be given her [Martha]. I could by no means bring her to own, That she desired the mercies of God, and the prayers of good men. I would have obtained a Sign of such a Desire, by her Lifting up her hand; but she stirr'd it not: I then lifted up her hand my self, and though the standers-by thought a more insignificant thing could not be propounded, I said, "Child, If you desire those things, let your hand fall, when I take mine away:" I took my hand away, and hers continued strangely and stifly stretched out, so that for some time, she could not take it down. During these days we had Prayers oftener in our Family than at other times; and this was her usual Behaviour at them. The man that prayed, usually began with Reading the Word of God; which once as he was going to do, she call'd to him, "Read of Mary Magdalen, out of whom the Lord cast seven Devils." During the time of Reading, she would be laid as one fast asleep; but when Prayer was begun, the Devils would still throw her on the Floor, at the feet of him that prayed. There she would lye and Whistle and sing and roar, to drown the voice of the Prayer; but that being a little too audible for Them, they [the devils] would shut close her Mouth and her ears, and yet make such odd noises in her Throat as that she herself could not hear our Cries to God for her. Shee'd also fetch very terrible Blowes with her Fist, and Kicks with her Foot at the man that pray'd; but still (for he had bid that none should hinder her) her Fist and Foot would alwaies recoil, when they came within a few hairs breadths of him just as if Rebounding against a Wall; so that she touch'd him not, but then would beg hard of other people to strike him, and particularly she entreated them to take the Tongs and smite him; Which not being done, she cryed out of him, "He has wounded me in the Head." But before Prayer was out, she would be laid for Dead, wholly senseless and (unless to a severe Trial) Breathless; with her Belly swelled like

a Drum, and sometimes with croaking noises in it; thus would she ly, most exactly with the stiffness and posture of one that had been two Days laid out for Dead. Once lying thus, as he that was praying was alluding to the words of the Canaanites, and saying, "Lord, have mercy on a Daughter, vexed with a Devil; there came a big, but low voice from her, saying, "There's Two or Three of them" (or us) and the standers-by were under the Apprehension, as that they cannot relate whether her mouth mov'd in speaking of it. When Prayer was ended, she would Revive in a minute or two, and continue as Frolicksome as before. . . .

VIII

Perhaps I have been bewitched into drawing false conclusions, but it seems clear to me that Martha Goodwin had resorted to hysteria mainly because of religious uncertainties and conflicts; and toward a better understanding why Puritan children felt insecure as they contemplated this world and the world hereafter it is now necessary to say something of the Puritan religion. It should go without saying that no sensible man attempts to ridicule any religion so long as it remains a force for good, but, on the other hand, it is important to examine the probable results of the impact of the Puritan religion on the minds of growing children if one wishes to fathom the disastrous events that took place in Salem.

Long before they attained the age of reason, Puritan children were made to learn the contents of John Cotton's catechism, called "Spiritual Milk for Babes, Drawn out of the Breasts of both Testaments, for their Souls Nourishment." Among the first things they learned were the dreadful consequences of Original Sin. All wickedness, all sufferings and diseases, all catastrophes were only manifestations of God's "Holy Anger" and "Holy Jealousy" because of the fall of Adam and Eve. This doctrine (the sixth question and answer in the catechism) that all children were "conceived in sin and born in iniquity" was later carried to its logical conclusion by the preachers of the early eighteenth century. When the Rev. Jabez Fitch found that over 90 per cent of all the deaths from "throat distemper" occurred among children, that to him was mathematical proof of the "woful Effects of Original Sin." The brilliant theologian Jonathan Edwards stoutly maintained that sinful children were more hateful than vipers because vipers had no souls. Whitfield literally screamed at his audiences that children were worse than rattlesnakes and alligators, which, he said, were also beautiful when small; and Benjamin Wadsworth said that "They're Children of Wrath by Nature, liable to Eternal Vengeance, the Unquenchable Flames of Hell. . . . Truly it behooves them most seriously to consider how filthy, guilty, odious, and abominable they are both by Nature and Practice."

There is an illustrative passage in the *Diary of Cotton Mather* dated Nov. 7, 1697:

> I took my little [5 year old] daughter, Katy, into my Study, and there I told my child That I am to Dy Shortly and Shee must, when I am Dead, Remember every Thing, that I now said unto her. I sett before her, the sinful . . . condition of her Nature, and I charged her to *pray in secret places* every day, . . . I gave her to understand that when I am taken from her, shee must look to meet with more Humbling Afflictions, than she does.

The literature of colonial times abounds in examples of early piety, instances of "joyful deaths" of children who had learned every word of the catechism, for the Puritans were eager to preserve these instances of holiness in order to impress their remaining children. Cotton Mather has left an account of the precocious Elizabeth Butcher, 2½ years old. "As she lay in the Cradle, she would ask herself that Question, What is my corrupt Nature? and would make Answer to herself, It is empty of Grace, bent into Sin, and only to Sin, and that continually." Many more examples of early piety are related by the Rev. John Brown in his account

of "remarkable deaths" during the great diphtheria epidemic in Haverhill. Epidemics, catastrophes or deaths of playmates seemed to be opportune occasions to impress on children that they were born under the wrath and curse of God. Here is an interview with a dying 7 year old child:

> Being ask'd if she was willing to die, and go to Christ; she said, Yes: But Child you know you are a Sinner; she said Yes: And you know where the Wicked go when they die; she said, Yes they are cast into Hell. And Being asked, if she was not afraid of going thither: she said No, for Christ is an all sufficient Savior, and He is able to save me I hope he will: Tho' I have not yet seen Christ, yet I hope I shall see him. . . .
>
> A while after she said, I am weary of this World, and long to be gone!

The most pitiful, yet most significant, aspect of this gruesome theology was that the children, once convinced that they were dreadful sinners by birth, could do absolutely nothing about it. There was no use in begging for mercy or forgiveness, because every good Puritan firmly believed in predestination. God, even before the creation of the earth, the sun, the moon and the stars, had already determined who were to be saved and who were to be damned, and no one on earth could be certain whether or not he was among the elect. If God was willing, the adults, by constant prayer and good works, might experience a salvation or a flooding of the soul with an irresistible grace, and with this came the joyful feeling that they were among the elect. But this involved a complex mental process that no child could experience, much less enjoy. And so, with the avenue to mental peace left open only to adults, thoughtful children became terribly bewildered. There are no more pitiful passages in all Puritan literature than those in Sewall's diary wherein he related the gloomy religious outlook of his daughter Betty:

> It falls to my [7 year old] daughter Elizabeth's share to read the 24. of Isaiah [which concerns the earth's turning upside down and the inhabitants thereof falling into space] which she doth with many tears not being well and the contents of the chapter and sympathy with her draw tears from me also. . . . .
>
> When I came in, past 7. at night, my wife met me in the Entry and told me Betty [13 years old] had surprised them. I was surprised with the abruptness of the Relation. It seems Betty Sewall had given some signs of dejection and sorrow; but a little after dinner she burst out in an amazing cry, which caus'd all the family to cry too; Her mother ask'd the reason; she gave none; at last she said she was afraid she should goe to Hell, her Sins were not pardon'd. She was first wounded by my reading a Sermon of Mr. Norton's, about the 5th of Jan. Text of Jno. 7. 34. Ye shall seek me and shall not find me. And those words in the Sermon Jno. 8. 21. Ye shall seek me and shall die in your sins, ran in her mind and terrified her greatly.

At the age of 16 Nathaniel Mather wrote in his diary: "When very young I went astray from God, and my mind was altogether taken with vanities and follies; such as the remembrance of them doth greatly abase my soul within me. Of the manifold sins which then I was guilty of, none so sticks upon me, as that being very young, I was whittling on the sabbath-day; and for fear of being seen, I did it behind the door. A great reproach of God! a specimen of that atheism that I brought into the world with me." When 19 years old, he confessed on his deathbed that the most bitter of all his trials on earth were "the horrible conceptions of God, buzzing about [his] mind."

It is needless to say much about Puritan conceptions of hell except that epidemics and earthquakes seemed to offer opportune moments for the publication of broadsides and sermons containing the most lurid descriptions. Children were taken on walks through cemeteries to see where other smaller children were buried, for a child was "never too little to die, and never too young to go to hell." The classic example of all this is Michael Wigglesworth's oft-quoted 224 stanza poem on "The Day of Doom" (1662), a work which went through numerous editions

and was familiar to nearly every Puritan child. In it are depicted the terrors of the damned in terms that might even today send shivers up the spine of the most confirmed atheistic pediatrician. Of some interest are Wigglesworth's ideas of the punishment inflicted on the newly born, or, as he expressed it, on those who went "from the womb unto the tomb." On the fateful Day of Doom those little infants, exceedingly reluctant to be cast into hell because of Adam's sin, put up a strenuous argument:

> Not we, but he ate of the tree
> whose fruit was interdicted:
> Yet on us all of his sad fall,
> the punishment's inflicted.

But all cases were predetermined, so the sentence was nevertheless pronounced:

> You sinners are, and such a share
> as sinners may expect,
> Such you shall have; for I do save
> none but my own elect.
> Yet to compare your sin with their
> who lived a longer time,
> I do confess yours is much less,
> though every sin's a crime.
> A crime it is, therefore in bliss
> you may not hope to dwell,
> But unto you I shall allow
> the easiest room in hell.

VIII

Enough has been told to show that the average Puritan child, if he paid any attention to the rigid Calvinism of the times, must have had gloomy prospects of life beyond the grave; and there can be little doubt that some of them at least lived in constant, gnawing fear not only of death but of eternal damnation after death. Thus the appearance of hysteria among the children of Salem Village has an adequate explanation, as it has in the numerous other case histories that are known. Preserved in the Puritan literature are many isolated instances of strange diseases among children which sound much like hysteria. Though perhaps not so dramatic, because there were no executions, but just as important are the examples of mass religious hysteria during the frequent revivals, of which the "Great Awakening" in 1740 is the best example. And it is a curious fact that no one ever blames the children for the outbreak of hysteria at Northhampton in 1740, yet the children of Salem are held responsible for what was an essentially similar affair. With a knowledge of the religious background of the Salem children it seems rather unimportant to argue whether Cotton Mather was guilty of the witchcraft hangings by influencing the governor, the judges or the mob on Gallows Hill. He was guilty only insofar as he was a Calvinist; but so, indeed, was nearly everybody else.

The history of the Salem witchcraft should be more concerned with the family background and medical history of the afflicted children, for they were victims as well as the persons who were hanged. It was no coincidence that Martha Goodwin, child of devout parents, acquired her hysteria just at the time when "she was in the dark concerning her Souls estate" and the mere sight of the Bible or the catechism always sent her into "hideous convulsions." Nor was it very strange that the first cases in Salem Village occurred in the very home of that red-hot Devil-chaser, the Rev. Samuel Parris. "Pray for the salvation of my soule for they will kill me," from the mouth of the bewitched Mercy Lewis, was one of the most significant remarks made during the Salem trials. Those children had ample reason to become hysterical when repeatedly told that the monstrous, invisible, venomous,

hissing and sooty Devil was right in their neighborhood ready to devour them; and no doubt many of them were positively convinced that they were actually bewitched.

One is not obliged to accept the verdict of the popular historians that the children were deceitful, wicked, malicious and dishonest. History has been unkind to them along enough. They were not imposters or pests or frauds; they were not cold-blooded malignant brats. They were sick children in the worst sort of mental distress—living in fear for their very lives and the welfare of their immortal souls. Hysteria was only the outward manifestation of their feeble attempts to escape from their insecure, cruel, depressive Salem Village world—a world thoroughly saturated with the pungent fumes of burning brimstone.

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Miller and Johnson [6] provided a bibliography of the Salem witchcraft in general, and Fleming [7] has included a bibliography of the religious background of Puritan children but not in relation to witchcraft. Cotton Mather's "Memorable Providences" has been reprinted by Burr.[8]

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Anatomy and Physiology

NORMAL STERNAL MARROW IN CHILDHOOD. VALDEMAR KORNERUP, Nord. med. (Hospitalstid.) **9**:416 (Feb. 8) 1941.

Examinations of sternal marrow from 34 children and 18 adults were made. It was found that the number of cells was greater in children (about 200,000) than in adults (average 114,000). The children had fewer segmented myeloid cells but more myeloblasts, erythroblasts and lymphocytes, and their cells showed mitosis to a greater extent. In the youngest children the number of myeloid cells increased by an increase of the mature segmented cells, while the myeloblasts became fewer. With advancing childhood the number of the erythroblasts decreased, and erythroblasts in the youngest stages were more and more infrequently seen at the same time that the lymphocytes decreased. Plasma cells could not be demonstrated during the first months of life and were only rarely detected during the first year; thereafter they increased in number until adult values were reached at about 10 years of age.

WALLGREN, Göteborg, Sweden.

MORPHOLOGIC DEVELOPMENT OF BONE MARROW IN FETAL LIFE. NILS G. NORDENSON, Nord. med. (Hygiea) **11**:2283 (Aug. 2) 1941.

Nordenson has studied the bone marrow in 83 fetuses. The parenchyma of the marrow is derived from the primitive angioblasts. The angioblasts develop out of the primitive reticular cell, which functions as the stem cell of the erythropoiesis as well as of the myelopoiesis and the thrombocytopoiesis. This primitive reticular cell is identical with the reticulum cell of the bone marrow in the adult. The erythropoiesis begins when the fetus has reached a length of 6 cm.; the myelopoiesis is established at a fetal length of 10 cm. The megakaryocytes are directly derived from the reticulum cells, and platelets appear at a fetal length of 10 cm. Neither lymphocytes nor monocytes develop from the reticulum cells of the bone marrow.

WALLGREN, Götebord, Sweden.

Biochemistry; Bacteriology, and Pathology

STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM: XVI. THE INFLUENCE OF THE PITUITARY GLAND. WALTER BAUER and JOSEPH C. AUB, J. Clin. Investigation **20**:295 (May) 1941.

Evidence concerning the relationships of the pituitary and parathyroid glands and calcium and phosphorus metabolism is reviewed, and data are presented on the calcium and phosphorus metabolism of 4 patients with varying grades of acromegaly and 1 with only slight evidence of increased pituitary activity. The patients with acromegaly had an increased urinary excretion of calcium and phosphorus, although the values for calcium and phosphorus in the blood and feces were normal. The increased rates of excretion roughly paralleled the intensity of the disease but did not depend on an elevated basal metabolic rate.

GUEST, Cincinnati.

ACID-BASE BALANCE, RENAL FUNCTION, AND GASTRIC SECRETION DURING HYPOCHLOREMIA IN THE DOG. JOSEPH B. KIRSNER and KATHRYN KNOWLTON, J. Clin. Investigation **20**:303 (May) 1941.

Chloride deprivation was produced gradually in 2 healthy dogs by the intermittent withdrawal of histamine-stimulated gastric juice over periods of seventy-four and eighty-six days. The gastric juice was withdrawn through a cannula from the stomach through the abdominal wall. The dogs received a generous diet, but with low salt content, and a liberal allowance of chloride-free water. A severe alkalosis and hypochloremia developed without marked retention of nitrogen. Such an alkalosis apparently did not produce renal injury. The secretion of hydrochloric acid by the gastric mucosa was relatively uninfluenced by the profound hypochloremia.

GUEST, Cincinnati.

THE CLEARANCE OF BILIRUBIN FROM THE PLASMA: A MEASURE OF THE EXCRETING POWER OF THE LIVER. A. A. WEECH, DOROTHEA VANN and ROSE A. GRILLO, J. Clin. Investigation **20**:323 (May) 1941.

As a measurement of excretory function of the liver, the rate of removal from the circulation of intravenously injected bilirubin is evaluated as a velocity constant. The velocity constant is computed in milligram units which express the rate of excretion from each 100 cc. of plasma in milligrams per minute per milligram-squared of concentration in the circulating plasma. A minimum of three determinations of serum bilirubin concentration is required for the calculation. The method of analysis is described in detail. GUEST, Cincinnati.

Metabolism; Infant Feeding; Milk and Other Foods

A COMPARISON OF THE VALUE OF CRYSTALLOID SOLUTIONS, WHOLE BLOOD AND BLOOD PLASMA IN THE TREATMENT OF DEHYDRATION IN INFANCY. A. G. V. ALDRIDGE, Arch. Dis. Childhood **16**:182 (Sept.) 1941.

A detailed study of dehydration in infants was carried out on patients with gastroenteritis and pyloric stenosis. Determinations of serum chloride, protein, hemoglobin and red cells and hematocrit readings were made before and after subcutaneous injections of physiologic solution of sodium chloride, intravenous injections of hypertonic solutions of dextrose, transfusions of whole blood and transfusions of plasma. From 8 to 14 infants were treated by each method. The author gives an excellent discussion of the results and concludes:

Physiologic (0.9 per cent) solution of sodium chloride should not be used for routine treatment of dehydration from gastroenteritis, since in many instances there is an apparent, if not actual, accumulation of chloride in the blood, which may increase if further chloride is administered. The routine use of whole blood in the treatment of dehydration is not recommended, as in the majority of cases the blood, which is already concentrated, becomes even more so after the transfusion. When the use of blood transfusion is considered, the hematocrit reading should be taken, and preferably the erythrocyte count and hemoglobin concentration should be estimated. If these are elevated above normal levels transfusion is unsuitable. In patients in whom the hematocrit shows a marked degree of hemoconcentration and who require more drastic treatment than the administration of crystalloid solutions parenterally, transfusions of plasma should be undertaken. KELLY, Milwaukee.

COMPLEMENTARY POWER OF BLOOD SERUM IN NUTRITIONAL DISTURBANCES OF INFANTS I. SERRA, Pediatria **49**:75 (Feb.) 1941.

The author determined the complementary power of the blood serum of 26 infants with various nutritional disturbances. He found that it was sharply decreased in most of the cases. The more serious the disease, the lower was the value.

MARTOCCIO, Utica, N. Y.

BLOOD SUGAR CURVES IN CHRONIC NUTRITIONAL DISTURBANCES. E. COMOLLI, Pediatria **49**:137 (March) 1941.

The author records the blood sugar curves for 25 infants aged from 5 months to 21 months. All were suffering from chronic nutritional disturbances. Low values were found in half of the tests, normal values in one fourth and high values in one fourth.

MARTOCCIO, Utica, N. Y.

THE USE OF PLANTAIN IN INFANTILE DIARRHEA. W. BUSTAMANTE, Rev. chilena de pediat. **12**:458 (June) 1941.

The plantain is a fruit well taken as an addition to the infant's diet and is a useful therapeutic agent in the benign diarrheas of infancy, especially when modified milk or a dietary regimen is not well tolerated. SCHLUTZ, Chicago.

INVESTIGATION CONCERNING STORED PROTEIN IN THE ORGANISM OF INFANTS AND CHILDREN: III. NORMAL TOTAL PLASMA PROTEIN VALUES CALCULATED FROM AVERAGE WATER CONTENT OF BLOOD CORRESPONDING TO AGE OF CHILD. P. UJSAGHY, Ztschr. f. Kinderh. **62**:483 (April 24) 1941.

The author reports plasma protein values (corrected in some measure for dilution or concentration of blood) for different periods of infancy (including infancy of the prematurely

born) and childhood. The hyperproteinemia of the first ten days of life is assumed to be attributable to destruction of blood and ingestion of colostrum. Values are higher for artificially fed than for breast-fed infants presumably because of the higher protein content of cow's milk. The gradual slow increase during childhood is presumably ascribable to a change in mode of life, particularly to the changed constituency of the diet.

SIEMSEN, Kalamazoo, Mich.

INVESTIGATIONS CONCERNING STORED PROTEIN IN THE ORGANISM OF INFANTS AND CHILDREN: IV. INVESTIGATIONS TO DETERMINE THE CIRCULATING RESERVE PROTEIN IN THE BLOOD PLASMA. P. UJSAGHY, Ztschr. f. Kinderh. **62**:496 (April 24) 1941.

Healthy infants fed carbohydrate diets practically free of protein presented several types of blood protein curves. Levels above 7 per cent were reduced to approximately 7 per cent immediately or after an initial increase. Levels around 7 per cent tended to remain approximately the same. In the cases of infants ill with colitis or dysentery the values dropped considerably below 7 per cent.

The author interprets his results as follows: The portion of the protein value in excess of 7 per cent represents stored protein; values below 7 per cent indicate that stored protein has been utilized and that organized protein has been broken down.

SIEMSEN, Kalamazoo, Mich.

FEEDING OF INFANTS WITH CITRIC ACID MILK. NILS MALMBERG, Nord. med. (Hygiea) **9**:528 (Feb. 15) 1941.

Undiluted citric acid milk is recommended in cases in which a concentrated feeding is indicated and as complementary feeding in the treatment of dyspepsia of breast-fed infants.

WALLGREN, Göteborg, Sweden.

IS BOILED BREAST MILK TO BE REGARDED AS AN APPROPRIATE INFANT'S FOOD? C. GERD BLUME-WESTERBERG, Svenska läk.-tidning. **38**:920 (April 18) 1941.

This is a report of metabolism studies on infants and premature children fed with raw or boiled breast milk. It was shown that boiled breast milk was well tolerated and that its albumin, fat and carbohydrates were resorbed as well as those of raw milk. The balance of sodium chloride, calcium and phosphorus showed somewhat lesser resorption than from raw milk.

WALLGREN, Göteborg, Sweden.

BREAST MILK SECRETION DURING THIRST AND DURING FORCED FLUID INTAKE. AXEL OLSEN, Ugesk. f. læger **103**:897 (July 10) 1941.

Thirteen mothers were examined. Even great variations of the quantity of fluids ingested by nursing women are generally without any effect on the daily supply of breast milk. The amount of fluids to be consumed may be left entirely to the physiologic regulation. The development of hypogalactia cannot be stopped by forced intake of fluid.

WALLGREN, Göteborg, Sweden.

Vitamins; Avitaminoses

EFFECTS OF VITAMINS B_1 AND C ON THE ENDOCRINE EQUILIBRIUM IN INFANCY. G. MURANO, Pediatria **49**:21 (Jan.) 1941.

The author reviews the literature concerning the effects of vitamins B_1 and C on the various endocrine glands in animals. In a group of infants no effect of vitamins B_1 and C on the endocrine equilibrium was noted.

MARTOCCIO, Utica, N. Y.

VITAMIN A SUPPLY OF THE FINNISH PEOPLE. P. E. SIMOLA and NIILO SAKSELA, Nord. Med. (Finska läk-sällsk. handl.) **9**:275 (Jan. 25) 1941.

This is a report on biophotometric investigations of the vitamin A levels of 1,377 persons from various classes of the population of Finland. It was found that in the neighborhood of the capital, Helsingfors, 66.5 per cent of the school children had normal values during the autumn, 18.3 per cent had subnormal values and 15.3 per cent had values that were in a transitional state. During the late winter months 58.2 per cent had normal values, 27 per

cent subnormal values and 14.8 per cent transitional values. The highest values for adults were found in soldiers at the front in the Finnish-Russian war; 87.5 per cent of these values were normal.

WALLGREN, Göteborg, Sweden.

ESOPHAGOSPASM AS A CAUSE OF SCURVY. ARVID WALLGREN, Svenska läk.-tidning. **38**:915 (April 18) 1941.

A neurolabile boy of 7, who had suffered from cardiospasm with severe vomiting during the last two months and had become highly emaciated (body weight 14 Kg.), displayed purpuric spots on the skin. These were due to decreased capillary resistance associated with avitaminosis C. Rapid recovery was produced with large doses of ascorbic acid. The vomiting disappeared after psychogenic treatment, and the boy was discharged in good health.

WALLGREN, Göteborg, Sweden.

ASCORBIC ACID CONTENT OF HUMAN MILK. E. MÖLLER-CHRISTENSEN and C. THORUP, Ugesk. f. læger **103**:31 (Jan.) 1941.

Determinations of the ascorbic acid content of milk from 55 lactating women were made during the first ten days after parturition. The percentage of ascorbic acid was less than 1 at birth, increased rapidly during the first four days to 4 to 5 and then was fairly constant.

WALLGREN, Göteborg, Sweden.

ASCORBIC ACID CONTENT OF PLACENTA, BLOOD FROM UMBILICAL VEIN AND COLOSTRUM. E. MÖLLER-CHRISTENSEN and C. THORUP, Ugesk. f. læger **103**:35 (Jan. 9) 1941.

Ten women were examined. The ascorbic acid content of the mother's blood (0.44 mg. per hundred cubic centimeters) is less than that of the colostrum (0.80 mg. per hundred cubic centimeters), which, in its turn, is less than that of the blood from the umbilical vein (1.06 mg. per hundred cubic centimeters). The placenta contained 7.3 to 14.1 (average 10.1) mg. of ascorbic acid per hundred grams of placental tissue.

WALLGREN, Göteborg, Sweden.

RICKETS AND COD LIVER OIL PROPHYLAXIS. PAUL DRUCKER, Ugesk. f. læger **103**:285 (March 6) 1941.

The vitamin D content of cod liver oil varies from 50 to 85 international units per gram (230 to 400 units per teaspoon of oil). The author concludes that infants need 2 teaspoons of cod liver oil daily as a prophylactic measure.

WALLGREN, Göteborg, Sweden.

THREE FAMILIAL CASES OF ATYPICAL LATE VITAMIN-RESISTANT RICKETS. J. FLAMAND CHRISTENSEN, Ugesk. f. læger **103**:880 (July 3) 1941.

A mother and her 2 children, aged 13 and 15 years, suffered from a generalized atypical disease of the bones which showed roentgenologic and clinical similarities to both rickets and Morquio's disease. The phosphorus level of the serum was 2 to 5 mg. per hundred cubic centimeters; the serum calcium level was normal and the phosphatase content of the blood was increased. There was no sign of renal disease. Treatment with massive doses of vitamin D_3 (250,000 to 500,000 international units) produced some improvement, but ordinary doses of vitamin D and of endocrine substances gave no results.

WALLGREN, Göteborg, Sweden.

Prematurity and Congenital Deformities

OCULAR HYPERTELORISM OF GREIG. E. A. VORISEK, Am. J. Ophth. **24**:928 (Aug.) 1941.

Vorisek defines hypertelorism as abnormally widely separated eyes said to be the result of maldevelopment of the sphenoid bone. He enumerates its characteristics and reports 4 cases, in 3 of which photographs or roentgenograms or both proved the diagnosis.

W. S. REESE. [ARCH. OPHTH.]

HEREDITARY CRANIOFACIAL DYSOSTOSIS. E. A. VORISEK, Am. J. Ophth. **24**:1014 (Sept.) 1941.

Vorisek reports 2 cases of hereditary dysostosis craniofacialis and gives the following summary:

"Two typical cases of Crouzon's disease without hereditary implications are reported. One boy, who was observed for 5½ years, had decompressions of both cranium and orbit with unexpected success. The other boy, observed for only 2½ years, most probably should have decompression at an early date." W. S. Reese. [Arch. Ophth.]

Congenital Malformation of Upper and Lower Extremities in Siblings with Different Fathers. Karl O. Von Hagen, Bull. Los Angeles Neurol. Soc. **6**:82 (June) 1941.

Von Hagen reports the case of a Negro child aged 22 months whose birth had been normal but all of whose extremities were severely deformed. There was a thumb on each hand, and on the right hand a finger was attached to a bony projection from the ulna at the wrist. On the left hand were two rudimentary fingers. The thighs were short and fixed in abduction and external rotation; the knees were poorly formed and the legs short. The feet were misshapen, and their soles pointed upward, with two toes on each foot. The deep reflexes were feeble in the upper and absent in the lower extremities.

The mother of the child had had a sister with an inverted foot. She had had 3 sons and 1 daughter by a previous union. One of the sons had deformities similar to those of the patient, and the other 2 had inversion of the feet without hypodactyly. Von Hagen believes that these deformities may have resulted from an acquired alteration in the maternal germ plasm, similar to the inherited anatomic defects observed by Bagg in the descendants of mice treated with roentgen radiation. Mackay, Chicago [Arch. Neurol. & Psychiat.].

Macrodactylia. A. Annecchino, Pediatria **49**:162 (March) 1941.

The author presents the case of a 5 year old boy with greatly enlarged fingers of the right hand. The index and middle fingers were enlarged. Roentgen examination showed the bones of the fingers to be enlarged also. Martoccio, Utica, N. Y.

Acute Contagious Diseases

An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis: Clinical and Epidemiological Observations. Gertrude Reyersbach, T. F. Lenert and Ann G. Kuttner, J. Clin. Investigation **20**:289 (May) 1941.

An epidemic of influenza due to a recently described influenza virus, influenza B (Francis, T., Jr.: *Science* **92**:405, 1940) affected 50 children in a relatively isolated group of rheumatic children. The clinical symptoms were mild, and no complications developed. A relative leukopenia was usually found on the first day of the disease. No evidence was obtained to suggest that the virulence of group A beta hemolytic streptococci of proved pathogenicity prevalent in the community was increased by this strain of influenza virus.

Guest, Cincinnati.

The 1937-1938 Epidemic of Acute Anterior Poliomyelitis in New South Wales, with Special Reference to Change in Age Incidence, Poliomyelitis During Pregnancy and Poliomyelitis Following Tonsillectomy. Karen Helms and W. J. Willcocks, M. J. Australia **1**:467 (April 19) 1941.

Helms and Willcocks discuss certain epidemiologic features of the 1937-1938 epidemic of acute anterior poliomyelitis in New South Wales. During the first nine months of 1937 the average monthly incidence was 2 cases. Between October 3 and October 30, 5 cases occurred in the metropolitan area and 7 in rural districts. Up to Sept. 30, 1938, there was a total of 711 cases. The epidemic reached its peak earlier in the metropolitan area than in the rest of New South Wales. A study of the meteorologic elements from October 1937 to September 1938 suggests that the temperature and absolute humidity curves exhibit the closest correlation with the increase and decrease in the number of cases. Humidity, commencing in the spring, attains a maximum in a midsummer month and then declines. A somewhat similar correlation was suggested in the incidence of seasonal rainfall in northern parts of New South Wales. In the metropolitan area, during the early weeks of the epidemic and while the weekly incidence was increasing, severe paralysis developed in a greater proportion of patients than during the later stages of the epidemic. In rural districts the tendency may be masked by the fact that a relatively small population is spread over a large

area. The number of deaths was greater in the rural districts at the beginning and at the height of the epidemic than in the later stages. In the metropolitan area there appears to be a tendency for the age group up to 4 years to be proportionately larger and the group more than 15 years of age to be proportionately smaller at the beginning of the epidemic than in its later stages. This tendency may be masked in rural districts for the same reason that the severity of paralysis was masked. The fatality rate in New South Wales was 2.5 per cent, or 17 deaths. For the rural districts it was 4.08 per cent, or 11 deaths. The oldest patient was 63 years and the youngest 7 months of age; 64 per cent of 601 patients were males and 34 per cent females. There were only 5 patients less than 12 months of age. The percentage of patients less than 10 years of age was greater in the metropolitan area (paralytic patients 76.8 per cent) than in rural districts (paralytic patients 53.5 per cent). In the 1937-1938 epidemic of poliomyelitis in New South Wales 5 patients contracted the disease during pregnancy—1 in the fifth, 2 in the sixth, 1 in the eighth and 1 in the ninth month of gestation. A study of these cases and of 13 others reported in the literature showed only 1 in which spontaneous abortion followed closely on the infection. In 13 of the 15 cases in which pregnancy continued beyond the seventh month, the delivery and the child were normal. In the other 2 cases cesarean section was performed because of respiratory paralysis. Poliomyelitis in pregnancy uncomplicated by respiratory paralysis is not an indication for interruption of the pregnancy. In the presence of respiratory paralysis during the last weeks of pregnancy, respiration may be facilitated by the removal of the fetus. Of the 711 patients, 7 were known to have undergone tonsillectomy and adenoidectomy from seven to twenty-two days prior to the onset of the illness. Bulbar and spinal paralysis developed in 3 of these 7 patients, 2 had paralysis of the palate, 1 had spinal paralysis with no evidence of bulbar involvement and 1 had the nonparalytic form of the disease. There were no deaths. A review of the literature supports the contention that operations on the throat and nose favor the development of poliomyelitis of the bulbar type. When this disease is prevalent, the risk of subsequent invasion by the virus should be well weighed before tonsillectomy or adenoidectomy is undertaken. J. A. M. A.

DIAGNOSIS OF SLIGHT MYOCARDIAL INSUFFICIENCY DURING CONVALESCENCE FROM DIPHTHERIA. V. MENGOLI, Pediatria **49**:121 (March) 1941.

The author studied the cardiac function in 100 children recovering from diphtheria. They ranged in age from 6 to 14½ years. At the time of examination none were suffering from serious signs of insufficiency. The time of onset of the illness to the time of examination varied from two to ten weeks. The subjects were made to climb a flight of twenty-two steps rapidly two times. Electrocardiograms were taken immediately before and after and also three minutes after exercise. Seventy-three per cent of the patients with electrocardiographic changes also had changes after exercise. Twelve per cent who showed no changes before did show changes after exercise. The author considers this a slight myocardial insufficiency which could not be found otherwise. MARTOCCIO, Utica, N. Y.

PRIMARY DIPHTHERITIC CONJUNCTIVITIS IN THE INFANT. B. V. RE and V. MUHLMANN, Arch. de oftal. de Buenos Aires **16**:261 (May) 1941.

Diphtheria in the nursing infant, which although rare is not exceptional, has distinguishing features.

After a brief reference to the usual localizations, of which the nasal is the most frequent, the authors detail a case of primary diphtheritic conjunctivitis in a nursing infant 17 days old. This is the second case reported in Argentina. The diagnosis was confirmed by the finding of Löffler's bacillus in the exudate and the corresponding objective and subjective symptoms, with absence of invasion of the nasal and pharyngeal mucosa. Complete recovery was obtained with the use of antidiphtheritic serum.

The frequency, etiology, symptomatology, treatment, pathology and pathogenesis in general are discussed. C. E. FINLAY [ARCH. OPHTH.].

ULCERATIVE LARYNGITIS AS A COMPLICATION OF MEASLES. CARLOS PEDRO MERCADINO and DONATO VIVOLI, Rev. otorrinolaring. **1**:38 (Sept.) 1941.

The authors discuss the pathology of ulcerative laryngitis occurring as a complication of measles. They consider, first, the appearance of the larynx in the stage of invasion. Here they observed merely a congestive phenomenon which extended into the larynx from the surrounding mucous membrane. The symptoms vary from mild hoarseness to severe stridulous laryngitis associated with dyspnea and severe fighting for breath. Second, during the stage of the erup-

tion, the eruption may cover the entire larynx and become a grave complication, since it may produce infiltration about the aryepiglottic folds and even extend to the subglottic region. Here, too, dyspnea and asphyxia may be so severe that the differential diagnosis from diphtheria is often difficult. Third, during convalescence the lesion is usually that of ulcerative laryngitis. This as a rule appears at the conclusion of the period of eruption, and the symptoms are merely an aggravation of those seen in the earlier stages. Hoarseness is present, progressing to complete aphonia; the cough is dry and painful; the expectoration is mucopurulent and often streaked with blood. The dyspnea, with pronounced supraclavicular retraction and rapid progression to suffocation, is evidence of severe inflammation of both the mucosa and the submucosa.

Pathologically, intense redness and swelling of the mucosa of the epiglottis, the false cords and the infraglottic region are noted. Small ulcers are often present on the posterior wall of the larynx. The ulcerations may become more or less extensive; they are always serpiginous and are usually localized to the posterior segments of the vocal cords and to the arytenoid cartilages. Simple erosions may be encountered on the free borders of the vocal cords, but if they are deep they may form small cavities in the vicinity of the arytenoid cartilages and the posterior plates of the cricoid cartilages and advance to the trachea.

The authors' observations are based on postmortem examinations in 5 cases of death occurring in a series of 4,219 patients who were admitted to the Muñiz Hospital from 1927 to 1940. As a result of this study, the authors came to the following conclusions: 1. The laryngeal lesions precede the appearance of bronchopneumonia and are the direct cause of the bronchopneumonia. The pneumonia does not occur as a result either of an infection or of aspiration. 2. It is impossible to establish an etiologic classification of all the infections and eruptive diseases which can produce lesions of the larynx. This is probably due to the extreme polymorphic character of the lesions, which may range from simple congestion to severe ulceration. 3. Contrary to former opinion, the ulcerative lesions most frequently occur in the upper portion of the laryngotracheal tract. 4. It is difficult in some cases to make a differential diagnosis from diphtheritic croup. Direct smears and direct laryngoscopic examination may be necessary to establish the diagnosis. Lastly, in those cases in which there is severe ulceration of the larynx with extensive involvement of the trachea and associated bronchopneumonia, little can be accomplished by intubation, tracheotomy or oxygen therapy. In such cases the outcome is, as a rule, fatal.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

"COCCIC DIPHTHEROIDS," A FURTHER FORM OF DIPHTHEROID ANGINA. B. KEMKES, Ztschr. f. Kinderh. **62**:511 (April 24) 1941.

The author points out that in a considerable number of cases of angina clinically indistinguishable from diphtheria cultures do not yield Corynebacterium diphtheriae but yield instead hemolytic streptococci or staphylococci. He proposes the term "coccic diphtheroid angina" for this disease.

SIEMSEN, Kalamazoo, Mich.

RECURRENCE OF SCARLET FEVER. JAMES SCHWIELER, Nord. med. (Hygiea) **11**:2205 (July 19) 1941.

During the years 1917 to 1939, 9,616 patients who had had scarlet fever were discharged from the hospital for epidemic diseases in Göteborg, Sweden. Two hundred and sixty of them produced in all 277 return cases, an incidence of 3 per cent (or 3.8 per cent if only families with one or more children below 16 years of age who had not had scarlet fever previously are included). There was no demonstrable correlation between recurrence and the time of isolation. The isolation period in the years from 1917 to 1938 was five weeks; in 1939 it was only four weeks.

WALLGREN, Göteborg, Sweden.

COMPULSORY HOSPITALIZATION OF SCARLET FEVER PATIENTS. GUNNAR FISCHER, Svenska läk.-tidning. **38**:712 (March 28) 1941.

Patients with even mild scarlet fever should be isolated in a hospital; it is better for the sick child with regard to complications, and it is better for the healthy persons in the environment, as in this way the transmission of the disease may be stopped.

WALLGREN, Göteborg, Sweden.

ELECTROCARDIOGRAPHIC EXAMINATIONS IN SCARLET FEVER. EJNAR ROELSEN, Ugesk. f. læger **103**:571 (May 1) 1941.

This is a report on electrocardiographic examinations of 216 patients with scarlet fever, of whom 108 manifested arthralgia. Thirty-six of the latter and 26 of the other patients

had pathologic electrocardiograms. The changes shown on the electrocardiogram consisted principally in auriculoventricular block, nodal rhythm, abnormal ST intervals and abnormal deflections of the T wave. The changes were of transitory character and were not combind with any evident clinical signs of cardiac damage. They are supposed to be due to a purely toxic influence on the myocardium or to an allergic reaction.

WALLGREN, Göteborg, Sweden.

SEROUS MENINGITIS AS A COMPLICATION OF SCARLET FEVER. GUNNAR NIELSEN, Ugesk. f. læger **103**:942 (July 17) 1941.

Nielsen reports on 6 cases of scarlet fever with aseptic serous meningitis as a relatively early complication. The spinal fluid was sterile and contained 27 to 367 cells, principally mononuclear leukocytes. Five of the patients suffered from polyarthritis at the same time. Recovery was reported in all cases.

WALLGREN, Göteborg, Sweden.

ACTIVE IMMUNIZATION AGAINST DIPHTHERIA. KNUD BOJLÉN, Ugesk. f. læger **103**:1107 (Aug. 28) 1941.

Of 40,000 children in Copenhagen vaccinated by three injections of the anatoxin of Ramon in 1928 to 1940, 350 contracted diphtheria, usually of a mild type. Only 3 vaccinated children died of diphtheria.

WALLGREN, Göteborg, Sweden.

Acute Infectious Diseases

OTOGENOUS TETANUS. SAMUEL ROSEN, Laryngoscope **51**:892 (Sept.) 1941.

Rosen reports a case of generalized tetanus complicating chronic purulent otitis media, with recovery of tetanus bacilli from the middle ear, indicating that the middle ear may be the focus of generalized tetanus.

A Negro aged 18 walked into the hospital, complaining of some pain in the right side of his face on chewing and of drooping of the right upper eyelid for four days. For the past two years his right ear had been discharging, and at times the discharge was foul. The temperature, pulse rate, respiratory rate and results of general physical examination were normal.

The right ear showed a large central perforation, through which a mass of red, swollen mucosa protruded and a moderate amount of mucopurulent material was discharged. There was no tenderness of the mastoid. The patient heard a moderately soft whisper. He had some weakness of the right side of the face. He could open his mouth to the limit, but on so doing complained of tightness in the region of the right mandibular joint. The following morning the facial weakness was more marked, and the patient could only half open his mouth. The next morning he was found in opisthotonos, with rigidity of the abdomen, some rigidity of the extremities and almost complete trismus. Generalized tetanic convulsions were precipitated by noise or movement. The spinal fluid was normal. Laryngeal spasm necessitated tracheotomy. The temperature rose to 104 F., and bilateral lobar pneumonia developed. Tetanus antitoxin was given intravenously, 100,000 units for two days and then 50,000 units for several days. This dose was later reduced to 20,000, to 10,000 and, finally, to 5,000 units every three days. Altogether, 795,000 units of antitoxin was given within four weeks. At the end of two weeks the temperature became normal and the tetanic spasms almost entirely disappeared. The right ear discharged throughout, and the perforation became larger. Cultures of the discharge from the right ear showed Bacillus tetani and Bacillus proteus, confirmed by animal inoculation. Since the ear was considered the focus of tetanus, a mastoidectomy was done. The mastoid bone cut easily and was found to be diploic and soft. Cultures just before operation, at operation and since operation were all negative for tetanus bacilli. The patient recovered.

WOOD, Newark, N. J. [ARCH. OTOLARYNG.]

STAPHYLOCOCCUS ANTITOXIN IN PLEURAL EXUDATES AND CEREBROSPINAL FLUID. GINO BROGI, Pediatria **49**:65 (Feb.) 1941.

The author determined the level of antitoxin in the pleural exudate of 14 infants and found it to be lower than that in the blood. In 29 subjects the level in the cerebrospinal fluid was found to be negligible. One patient with ventricular empyema showed a high level of antitoxin in the ventricular fluid and a slight amount in the spinal fluid, while in the blood serum the level was also high.

MARTOCCIO, Utica, N. Y.

PERITONITIS DUE TO PERFORATION OF THE BILIARY VESICLE IN THE COURSE OF TYPHOID FEVER ACCOMPANIED BY SUPPURATIVE PAROTITIS. H. FERRER, H. J. NOTTI and A. GRINFELD, Arch. argent. de pediat. **15**:579 (June) 1941.

The authors report a case of this interesting condition in an 11 year old child. The perforation occurred in the course of an attack of typhoid fever and resulted in local peritonitis.

An abdominal operation revealed the perforation and a beginning general peritonitis. A few days after the operation a purulent parotitis developed. This was drained. After a stormy course of a few weeks the child made a complete recovery.

SCHLUTZ, Chicago.

A SMALL EPIDEMIC OF TRANSIENT PULMONARY INFILTRATIONS. HEDVID ADLERCREUTZ, Nord. med. (Hygiea) **11**:2397 (Aug. 16) 1941.

Adlercreutz reports on 7 cases of transient pulmonary infiltration (8 per cent eosinophils in 2 cases) developing with symptoms of an acute febrile infection which occurred in a small village from March to July. Four of the patients were children, 3 of whom were siblings, whose mother also fell ill with the same symptoms.

WALLGREN, Göteborg, Sweden.

INFLUENZAL MENINGITIS AND ITS TREATMENT. HERBERT HATHHORST, Svenska läk.-tidning. **38**:921 (April 18) 1941.

Hathhorst reports on 13 cases of Pfeiffer meningitis in children, 4 of whom were treated with sulfapyridine. Two of the latter children (of school age) recovered; the other 2, who were small infants, died. The author stresses the importance of early treatment.

WALLGREN, Göteborg, Sweden.

WEIL'S DISEASE. BERNDT MALMGREN, Svenska läk.-tidning. **38**:1546 (July 25) 1941.

Weil's disease often appears as an atypical acute infection, which may be combined with signs that for the inexperienced physician lead rather to a wrong than to a correct diagnosis, as, for example, the development of intense renal irritation, occasionally macroscopic hematuria, meningitis and catarrhal respiratory symptoms. The diagnosis therefore cannot and should never be based solely on clinical findings. The diagnosis of Weil's disease must be etiologic, by demonstration of leptospiras or by a serologic test analogous to Widal's reaction. In 104 cases observed by the author only 51 patients had jaundice.

WALLGREN, Göteborg, Sweden.

PERIARTERITIS NODOSA. SIGNE BANKE, Ugesk. f. læger **103**:532 (April 24) 1941.

An 8 year old boy fell ill with signs of subacute polyarthritis, fever and an eruption of pea-sized reddish blue papules localized to the extensor side of the elbows and knees. Biopsy disclosed arteritis and periarteritis. Tests of the blood revealed an increased sedimentation rate and a negative Wassermann reaction. His reaction to tuberculin was negative. The urine, the blood and the heart and abdominal organs were not abnormal. The boy was kept under clinical observation for one year, and slight improvement was noted. New nodules appeared while the older ones gradually disappeared, leaving a pigmented spot such as is observed after a hematoma.

WALLGREN, Göteborg, Sweden.

Chronic Infectious Diseases

HEREDITARY SYPHILIS OF THE EAR. E. ESCAT, Oto-rhino-laryng. internat. **25**:113 (Aug.) 1941.

In 1930 Escat reported to the Société de Médecine of Toulouse, France, his observations in 104 cases of hereditary syphilis of the auditory apparatus and compared these cases with 93 cases of acquired syphilitic otopathy. The essay was never published. In the ten years since 1930 he has observed 36 additional cases; the triad of Hutchinson was present in only 10 per cent of the 104 cases. In the first group there were 81 cases of impairment of hearing from labyrinthitis or from meningoneuritis; in the remainder the diagnosis was gumma of the tympanum and mastoid. The Bordet-Wassermann reaction was positive in 23 of 44 cases; the triad of Hutchinson was present in only 10 per cent of the 104 cases. The insidiousness of this form of syphilis, the sole symptom often being deafness, and the difficulties of diagnosis are emphasized. Characteristic are perceptive deafness, accompanied by early deficiency

of bone conduction with relatively good hearing for voice, lack of tinnitus, presence of Hennebert's syndrome, paralyses of the oculomotor and facial nerves (more frequently seen than in other forms of otopathy) and, frequently, negative reactions to the Wassermann test.

Extreme caution must be exercised in the use of arsphenamine preparations because of the danger to Corti's organ. It is preferable to inaugurate the treatment with mercury or bismuth salts.

Combining the two groups of patients one finds that 77 of them were females and 63 males; 40 patients were improved, 12 notably. The relatively poor results of therapy in congenital aural syphilis are to be attributed to delay of diagnosis rather than to inefficacy of the methods of treatment.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

PRIMARY TUBERCULOUS INFECTION IN INFANCY. N. CAMPANELLA, Med. ital. **22**:70 (Feb.) 1941.

The author reports the cases of 94 children under 2 years of age, all with a positive reaction to tuberculin. The mortality in this group was 38.4 per cent. The younger the child, the higher the mortality. The majority of the infants died of miliary tuberculosis or of meningitis. The best method of discovering the disease early is to do a tuberculin test. The best method of distinguishing between primary tuberculous infection and reinfection in an older child is to take serial roentgenograms.

MARTOCCIO, Utica, N. Y.

PRIMARY TUBERCULOUS INFECTION IN INFANCY. N. CAMPANELLA, Med. ital. **22**:114 (March) 1941.

Perifocal tuberculous infiltrations can be divided into four groups according to the roentgenograms: perifocal infiltration itself, epitubercular infiltration, perihilar infiltration and paratracheal infiltration. In the first two years of life the author found 22 cases of typical perifocal infiltration. In 13 of these the infiltration was perihilar and in the others epitubercular or perifocal. The most characteristic manifestation in the second period of infancy is a perihilar infiltration.

MARTOCCIO, Utica, N. Y.

HEREDITY AND TUBERCULOSIS. L. FRANZI, Med. ital. **22**:150 (April) 1941.

The author reviews the principal articles of the present time on heredity and tuberculosis. Endogenous factors are always secondary to environmental factors.

MARTOCCIO, Utica, N. Y.

VENEREAL LYMPHOGRANULOMA IN CHILDREN. MOGENS WINGE, Nord. med. **9**:807 (March 15) 1941.

Winge reports the cases of 2 girls, 16 and 13 years of age, suffering from lymphogranuloma venereum, probably infected by their mothers. In both children there were stricture of the rectum and hydrops of the knee joints; in one of them, in addition, a left-sided coxitis. The latter girl died after rectal operation. The author presents a table of the hitherto published 20 cases of inguinal lymphogranuloma in children (18 patients being girls). Eleven of the patients suffered from rectal stricture, 9 from inguinal adenitis, 6 from arthritis and 2 from erythema nodosum.

WALLGREN, Göteborg, Sweden.

PERCUTANEOUS (ROSENTHAL) METHOD OF BCG VACCINATION. KONRAD BIRKHAUG, Nord. med., Norsk mag. f. lægevidensk. **10**:1224 (April 19) 1941.

Experimental studies on guinea pigs and clinical vaccinations on adults (246 cases) and children (38 cases) with Rosenthal's multiple puncture method of BCG vaccination have given satisfactory results as regards development of sensitivity to tuberculin and freedom from untoward local reactions.

WALLGREN, Göteborg, Sweden.

CALMETTE VACCINATION OF YOUNG PERSONS. ARVID WALLGREN, Svenska läk.-tidning. **38**: 1473 (July 11) 1941.

With decreasing frequency of tuberculous infections in childhood the risk of primary tuberculosis in the tender adolescent age is increased, and, at the same time, there is an increase in acute forms of pulmonary tuberculosis in this age group. When adolescent boys and girls leave their parents' home in order to continue their studies at the university or to enter some professional school or to be trained at a military camp, they often come into contact with persons who have tuberculosis and are infected. It is therefore recommended that school

children who react negatively to tuberculin be vaccinated with BCG before they leave school. This is done in some Swedish districts, and the results are good.

WALLGREN, Göteborg, Sweden.

Diseases of Blood, Heart and Blood Vessels and Spleen

ACUTE HEMOLYTIC ANEMIA FROM THE SULFONAMIDES. CHARLES L. FOX JR. and REUBEN OTTENERG, J. Clin. Investigation **20**:593 (Sept.) 1941.

Within a year the authors observed 9 cases of acute hemolytic anemia, with 6 deaths, in the course of sulfanilamide or sulfapyridine therapy. Laboratory studies in 4 of these cases are reported. The red cells that survived hemolysis appeared to be essentially normal, containing little methemoglobin or sulfhemoglobin. Three pigments were found in the serum: hemoglobin, methemoglobin and Fairley's new pigment, methemalbumin. Comparisons of the amounts of hemoglobin liberated with the amounts left in the circulation and excreted by the kidneys indicated that the body could remove some 500 to 700 Gm. of hemoglobin rapidly from the circulation without the aid of renal excretion. Shock was a prominent symptom, most marked in the fatal cases. In the latter, the hemolyzed cells represented about 30 per cent of the total blood volume. This much reduction in volume of blood resulting from the rapid removal of the products of hemolysis, was thought to be a factor in hemolytic shock.

GUEST, Cincinnati.

DISEASES OF THE BLOOD AND HEMOPOIETIC ORGANS IN THE INFANT. F. TECILAZIC, Med. ital. **22**:164 (April) 1941.

This is a clear and concise description of the various forms of leukemia and several forms of erythroleukemia (leukemia in which immature red blood cells and granulocytes are found in the circulation).

MARTOCCIO, Utica, N. Y.

INFECTIOUS MONONUCLEOSIS. L. ROSSI, Pediatria **49**:149 (March) 1941.

The author presents 2 cases of infectious mononucleosis. He gives a clear, concise description of the history, clinical course and differential diagnosis of the disease.

MARTOCCIO, Utica, N. Y.

RESULTS OF SPLENECTOMY IN TWO CASES OF ERYTHROBLASTIC ANEMIA. M. ACUNA, Arch. argent. de pediat. **16**:126 (Aug.) 1941.

The author reports 2 cases of erythroblastic anemia, one patient being a child of 15 years and the other a child of 9 years. In both of these children the condition of erythroblastosis had been diagnosed and had existed since birth. Both of them had a splenectomy, the older child at the age of 5 years and the younger at the age of 10 months.

A prompt improvement followed immediately in the blood picture and in the general condition of the children. This improvement, however, was only transitory. Both children were considerably dwarfed and showed some mental retardation. The blood picture was unchanged. Both cases ended fatally.

The author concludes that splenic extirpation will prolong the life of patients with erythroblastic anemia but will not effect any definite improvement or cure.

SCHLUTZ, Chicago.

GAUCHER'S DISEASE IN AN INFANT. M. A. F. TOSCO, Bol. Soc. cubana de pediat. **13**:252 (May) 1941.

Tosco reports a case of acute Gaucher's disease in an infant. The symptoms began in the first week of life and were characterized by the development of the classic neurologic syndrome described in this disorder and enormous hepatosplenic enlargement, such as is generally seen only in older children and adults.

The author is of the opinion that intensive vitamin therapy was of some value in the case, and he recommends particularly the use of vitamin A.

SCHLUTZ, Chicago.

A CASE OF ACUTE HEMOLYTIC ANEMIA. L. G. STERNER, Nord. med. (Hygiea) **9**:524 (Feb. 15) 1941.

An 8 month old breast-fed girl fell acutely ill with fever, jaundice, vomiting and diarrhea. When first seen, on the fourth day of the illness, she was extremely pale. Examination of

the blood showed: hemoglobin content, 31 per cent; red cells, 1,750,000; white cells, 13,700; and thrombocytes, 48,000. The fragility of the red corpuscles was within normal limits. Nucleated erythrocytes were present. The urine contained albumin, sugar and abundant red cells. The Wassermann reaction was negative; the spleen was not palpable. The child was given three intra-abdominal injections of blood. Recovery was rapid, and she was discharged from the hospital three weeks later with a normal blood picture.

WALLGREN, Göteborg, Sweden.

ACUTE HEMOLYTIC ANEMIA IN A CASE OF ACUTE HEPATITIS. KNUT KJELLBERG, Svenska läk.-tidning. **38**:924 (April 18) 1941.

A boy of 5 years suffering from acute hepatitis (catarrhal jaundice) fell ill three weeks after the onset of this disease with a rapid developing hemolytic anemia of Lederer's type. The hemoglobin content decreased from 76 per cent to 27 per cent, and the red blood corpuscles fell to 1,450,000. Recovery occurred after blood transfusions.

WALLGREN, Göteborg, Sweden.

HAS CHLOROSIS REALLY DISAPPEARED? JAN WALDENSTRÖM, Svenska läk.-tidning. **38**:1613 (Aug. 8) 1941.

The author has studied 26 cases of so-called essential hypochromic anemia in female patients of less than 25 years of age and stresses the clinical and hematologic resemblance of the disease to chlorosis. The leading sign in these two groups of anemias is a marked sideropenia and rapid response to treatment with iron. He considers chlorosis to be the juvenile manifestation of the sideropenic disease. This is very rare in young women in rural districts but rather common in some urban districts in Sweden.

WALLGREN, Göteborg, Sweden.

FIBRINOPENIA IN WOMEN WITH PREMATURE DETACHMENT OF THE PLACENTA. H. DAM, H. LARSEN and P. PLUM, Ugesk. f. læger **103**:257 (Feb. 27) 1941.

In 2 cases of premature detachment of the placenta the fibrinogen content of the blood was considerably reduced as compared with the content in normal pregnant and parturient women. It is suggested that the fibrinopenia causes the hemorrhagic diathesis, which is the cause of the apoplexia uteroplacentaris.

WALLGREN, Göteborg, Sweden.

Diseases of Nose, Throat and Ear

CLINICAL CONDITIONS ARISING FROM ANOMALIES OF MALDEVELOPMENTS OF THE BRANCHIAL ARCHES OR CLEFTS. WALTER B. HOOVER, Ann. Otol., Rhin. & Laryng. **50**:834 (Sept.) 1941.

Hoover reports on material gathered largely from the Lahey Clinic with respect to (1) variations in the right recurrent laryngeal nerve and the great vessels in the upper portion of the chest and the neck; (2) epidermal inclusion (dermoid) cysts; (3) preauricular sinuses, supernumerary cartilages about the ear and maldevelopment of the auricle, external auditory meatus and middle ear; (4) lateral cervical branchiogenic cysts and sinuses, and (5) anomalies of the thyroglossal tract and aberrant thyroid. These conditions are all briefly discussed and the management discussed. The direct innervation of the larynx from the vagus nerve by way of the inferior laryngeal nerve on the right side and the anomalous development of the right subclavian artery from the arch of the aorta on the left, so that it crosses behind the esophagus and presses on it, occur with sufficient frequency that laryngologists should keep the possibility in mind.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

ACUTE LARYNGOTRACHEAL BRONCHITIS: CURE BY ENDOSCOPIC THERAPY. M. GONZÁLEZ LOZA, Rev. otorrinolaring. **1**:11 (Sept.) 1941.

González Loza discusses the histopathology, symptomatology, diagnosis and treatment of acute laryngotracheal bronchitis in children. He presents 2 cases in detail in which cure was effected with endoscopic treatment. He concludes: 1. Acute laryngotracheal bronchitis is a clinical entity. 2. It is both a contagious and a seasonal infection, the appearance of which is often coincident with epidemics of grip and diphtheria. 3. The disease occurs relatively constantly in the part of Argentina with which the author is familiar, but it is often unrecognized by the internist and the pediatrician. 4. The condition is easily confused with other acute infections of the respiratory tree. The internist can make only a tentative diagnosis,

but the directoscope provides the one method by which one can make the diagnosis with certainty. 5. Endoscopic examination should be obligatory in all cases of suspected laryngotracheal bronchitis, especially in children. 6. The therapeusis in this disease is essentially of a mechanical order and should be directed toward the obstructive factor. Aspiration of the secretion with or without the instillation of a cajuput oil from Melaleuca viridiflora (gomenol) is the method of preference. 7. Bronchoscopy has fundamentally altered the prognosis in this disease. Whereas formerly there was a mortality of 100 per cent, many cures are now effected, especially when the patient is seen early and there is no opportunity for extensive destruction of the tracheobronchial tree.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

MASTOIDITIS AND THE SEDIMENTATION TEST. JUAN B. ARCIONI and HORACIA E. L. QUEROL. Rev. otorrinolaring. **1**:78 (Sept.) 1941.

Arcioni and Querol found that the sedimentation rate is always increased in surgical mastoiditis, running between 65 and 90 mm. and between 99 and 125 mm. for the first and second hours, respectively, with an average of 77.5 and 107 mm., respectively. This is true with respect to what they term the fibroconnective phlegmons. With empyema of the mastoid, the values range from 17 to 86 mm. and from 31 to 110 mm. for the first and the second hour, respectively, with a mean of 51.5 and 70.5 mm. In the cases of thrombophlebitis they found the rate to be 35 mm. the first hour and from 43 to 60 mm. the second hour. Normally, fifteen to twenty days after the operation the sedimentation rate returns to normal. With any complication there is always an increase in the curve. They consider the normal rate as 10 mm. for the first hour and 14 mm. for the second hour. The clinical gravity, however, does not depend on the intensity of the drop in the sedimentation rate. The well pneumatized mastoid always gives a higher rate, while the sclerotic mastoid gives a normal and localized empyema usually gives a lower than normal rate.

PERSKY. Philadelphia. [ARCH. OTOLARYNG.]

INFLUENCE OF TONSILLECTOMY ON THE BLOOD PICTURE. E. URBANTSCHITSCH, Monatschr. f. Ohrenh. **74**:397 (July) 1941.

Within two hours after tonsillectomy leukocytosis appears, with a definite shift to the left, usually lasting for three days. Increase in young forms and rod forms of granulocytes and a decrease in lymphocytes usually follow. Destruction of the granular elements and unripe forms have also been observed. The studies were carried out on 41 patients.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

TONSILLECTOMY IN CHILDREN. ERWIN SCHIFF, Pract. oto-rhino-laryng. **3**:358, 1941.

Schiff, in a detailed discussion of the pros and cons of indiscriminate and generalized tonsillectomy in children, takes the stand that this operation has been performed too frequently. After citing the observations of several investigators, particularly Kaiser, he expresses the belief that tonsillectomy is indicated only in selected cases. His indications are (1) frequent attacks of angina and peritonsillar abscess, and (2) pronounced and permanent hypertrophy of the tonsils, which, though they do not act as a focus of infection, interfere with the proper feeding of the child.

Tonsillectomy for the sake of removal of a focus of infection is definitely contraindicated, since there is no substantial evidence that the tonsils can produce focal symptoms. Here he is citing Reimann. He believes that the danger of pulmonary abscess or hemorrhage, the bad effect of narcosis and the greater liability of catarrhal inflammation of the respiratory tract in tonsillectomized children are sufficient to lead the rhinologist to exercise greater forbearance in the general recommendation of this operation.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

DIAGNOSTIC SIGNIFICANCE OF THE AUDIOGRAM IN CASES OF IMPAIRED HEARING. LUDWIG STERN, Ztschr. f. Hals-, Nasen- u. Ohrenh. **47**:150 (Dec.) 1940.

Stern, in evaluating the significance of the various curves of a series of audiograms, attempted to establish a typical curve as a diagnostic index to the different types of hearing impairment. He classified the types of hearing loss as: (1) conductive impairment, with changes in the tympanic membrane; (2) otosclerosis; (3) deafness arising in the internal ear; (4) mixed deafness; (5) central deafness, and (6) deafness due to injuries to the skull. He found that there was a close parallelism between the audiometric features and the clinical diagnosis and that there did not appear to be a frank contradiction in a single case. The audiogram had particular significance in cases of otosclerosis.

A comparison of the audiogram and the results of the spoken voice tests also showed a close similarity, except in cases of internal ear deafness, in which the spoken voice test showed a variance. It is with this type of hearing impairment that the audiogram is of signal importance, since it can often detect an early alteration of hearing acuity. The author finally discusses the significance of the high tone (c-5) dip, which is present in many audiograms. This may be isolated either in a pathologic or in an apparently normal ear. This dip suggests early involvement of the inner ear. This cochlear degeneration may have a hereditary, an idiopathic, a toxic or a traumatic source. If traumatic, it is likely to be due to an acoustic rather than a mechanical form of trauma. PERSKY, Philadelphia [ARCH. OTOLARYNG.].

EFFECT OF NOISE ON NORMAL AND IMPAIRED HEARING. P. WEERSMA, Ztschr. f. Hals-, Nasen- u. Ohrenh. **47**:402 (Feb.) 1941.

Weersma studied the masking effect in audiometry. This is an important aid, but its use must be understood. If the tone to be masked is lower than the masking tone, the effect of the latter is negligible. If the two tones are relatively close, the masking action is most effective. Finally, if the masking tone is lower than that tested, the results have no significance.

The author constructed a special instrument which would produce a masking effect at different frequencies. He found that the audiogram of both normal and impaired hearing presented a new form of curve, with "dips" that were frequently missed by the usual method of examination. PERSKY, Philadelphia [ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura and Mediastinum

ROENTGENOLOGIC DIAGNOSIS OF ACUTE BRONCHIOLITIS (CAPILLARY BRONCHITIS) IN INFANTS. LESTER W. PAUL, Am. J. Roentgenol. **45**:41 (Jan.) 1941.

The pathologic and clinical aspects of acute bronchiolitis are carefully and thoroughly reviewed in relation to the literature. Four cases are reported.

Roentgenologically the earliest and most consistent finding was a uniform bilateral emphysema with a narrowing of the cardiac borders and depression of both diaphragmatic leaves. No mediastinal shift was seen. There was also an increase in hilar markings, and later patchy areas of pneumonic consolidation were superimposed on the general picture of emphysema. It is pointed out that the early roentgenologic picture is identical with that of a ball valve obstruction of the trachea by a foreign body, and the two conditions must be differentiated by clinical findings and, if necessary, bronchoscopy. SQUIRE, Chicago.

ATELECTASIS AND BRONCHIECTASIS, AN EXPERIMENTAL STUDY CONCERNING THEIR RELATIONSHIP. JOSEPH TANNENBERG and MAX PINNER, J. Thoracic Surg. **11**:571 (Aug.) 1941.

In extensive experimentation on animals the authors found that: (1) pulmonary atelectasis due to obstruction of the bronchus from within may exist for periods up to several months without complications if no infection intervenes; (2) uncomplicated atelectasis tends to constrict, not dilate, the bronchi; (3) the increase in negative pressure on the side of the atelectasis exerts no dilating effect on the bronchi but does, however, account for the shift to the affected side; (4) infection superimposed on bronchial obstruction produces bronchiectasis; (5) ligation of the pulmonary artery does not produce bronchiectasis unless infection supervenes, and (6) finally, bronchiectasis is an inflammatory infiltration of the bronchial walls with accumulation of exudate in the bronchial lumens, which is prevented from draining because of artificially produced bronchial obstruction. DORSEY, Chicago.

A METHOD OF TREATMENT OF LARGE PULMONARY AIR CYSTS (BALLOON CYSTS) BY AN ENDOCUTANEOUS FLAP. A. LINCOLN BRON and WILLIAM BROCK, J. Thoracic Surg. **11**:617 (Aug.) 1941.

The authors state that pulmonary cysts are largely congenital malformations. Their subsequent course depends on whether or not they have a bronchial communication and the presence or absence of infection. These cysts may be intraparenchymal and, if so, may be removed by lobectomy or pneumonectomy. However, this presupposes the removal of potentially functional lung tissue.

That these cysts do need treatment other than needle aspiration or tube drainage is pointed out by the case history of a 41 year old man who complained of recurring attacks of extreme

shortness of breath. A balloon cyst was demonstrated. Drainage was instituted, and an endocutaneous flap was introduced directly into the cyst (after Eloesser) to prevent the recurrence of positive pressure within the cyst. The surrounding parenchyma expanded and became aerated.

DORSEY, Chicago.

TRACHEOBRONCHITIS COMPLICATING GRIP AND ITS TREATMENT. HANS LEICHER, Ztschr. f. Hals-, Nasen- u. Ohrenh. **47**:111 (Dec.) 1940.

The author discusses tracheobronchitis as a complication of grip and differentiates three stages: (1) simple tracheobronchitis, characterized by redness and swelling of the mucous membrane, with moderate mucoid secretion; (2) hemorrhagic tracheobronchitis, characterized by punctate hemorrhages throughout the mucous membrane, but without any interference with respiration, and (3) obstructive dry hemorrhagic tracheobronchitis. There are no pathognomonic features in the second stage, and consequently a differential diagnosis from measles and scarlet fever is difficult.

Of a series of 510 cases, Leicher was able to make a direct tracheoscopic examination in 260. In 71 per cent of his cases the condition was in the first stage, in 29 per cent in the second stage and in only 2 cases in the third stage.

He discusses the last 2 cases in detail. In 1 case he performed tracheotomy and inserted a tube, through which he removed the thick crusts that obstructed the airways, while in the second case he was able to remove the obstructing masses through a tracheoscope. Both patients recovered, but he stressed the seriousness of this complication, the gravity of the prognosis and the high mortality, death being usually due to bronchopneumonia.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

CASE OF PULMONARY AGENESIS. PER SELANDER, Svenska läk.-tidning. **38**:383 (Feb. 14) 1941.

Selander reports the case of a full term boy first seen at 6 months of age in connection with an acute infection. The right side of the thorax made no respiratory movements; there was a pronounced suction along the costal margin and rapid breathing; the percussion sound was dull on the whole right side of the thorax, and there was no respiratory murmur. The heart sounds were on the right side. Roentgen examination revealed a dense shadow occupying the right side with total displacement of the heart to the right. The patient was discharged in good health with remaining clinical and roentgenologic manifestations. He was last seen at 18 months of age, with the same signs and still free from respiratory symptoms.

WALLGREN, Göteborg, Sweden.

PSEUDOCAVERNS. H. SCHEUERMANN, Ugesk. f. læger **103**:110 (Jan. 23) 1941.

Scheuermann reports on 2 cases of pseudocaverns in small children following acute pneumonia. In one of the cases the "cavern" still persisted two years after its appearance; the child was in perfect health. In the other case the child died from pneumothorax due to rupture of the "cavern."

WALLGREN, Göteborg, Sweden.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

VOMITING FROM POSTOPERATIVE INFLAMMATORY REACTION IN INFANCY. GRENET, DESNOYERS, LABEAUME, VIGUIE and AUPINEL, Bull. Soc. pédiat. de Paris **37**:519, 1940.

These clinicians report 2 cases of vomiting due to a postoperative inflammatory reaction. The first case is that of an infant presenting at birth a large umbilical hernia, who was operated on under general anesthesia six hours after birth. Recovery was prompt and satisfactory, but on the seventeenth day a mass was noted in the right hypochondrium, oblong, dull on percussion and painless. There was explosive vomiting with much bile. Roentgen examination revealed no fasting residue in the stomach; there was an irregularity in this organ corresponding to the tumor mass just described. After the child had lost considerable weight, the condition improved under careful feeding and ventral decubitus, and within three weeks complete recovery was announced.

The second case was that of a girl of 2 months with a history of vomiting from birth. This vomiting followed no pattern; it might occur immediately after nursing or a considerable time later and was repeated several times daily. The general condition was not good. A provisional diagnosis of pyloric stenosis was made, and antispasmodics were prescribed.

For a short time these agents were effective, but the vomiting then recurred, with pronounced loss of weight. Operation showed complete absence of pyloric stenosis, but a small pylorotomy was made. Vomiting continued, and the weight dropped to 3,840 Gm. Although a serologic examination for syphilis showed no evidence of the disease, specific treatment was instituted; injections of whole blood were employed, and breast milk was used exclusively. The baby rested entirely in the ventral position. By the third month there was satisfactory recovery.

AMESSE, Denver.

VOMITING CAUSED BY ANOMALY OF THE DUODENUM. H. GRENET, GAUTHERON and AUPINEL, Bull. Soc. pédiat. de Paris **37**:547, 1940.

Vomiting of duodenal origin has not received extended consideration. A case of this condition was presented by the authors at a meeting of the Pediatric Society of Paris on May 21, 1940. A boy of 3½ years was admitted to the hospital with a history of vomiting accompanied by severe abdominal pain. While general in character, the pain was most intense in the epigastric region and was occasionally attended with fever. The stools were normal. The history showed that three days previous to admission there was a sudden accentuation of these symptoms; the vomitus contained bile; the patient was prostrated and somnolent, but groaning constantly. He lay doubled up on his left side; the abdomen was soft and without reaction to deep pressure; rectal examination revealed no abnormality. The reaction to tuberculin was negative, and the spinal fluid was normal. The chest was normal on roentgen examination. The urine, while scant, was free of all pathologic elements. For the first forty-eight hours in the hospital, the condition of the boy grew worse and the dehydration increased. Palpation of the abdomen now revealed a soft mass, not clearly limited, in the epigastrium. Percussion brought out a sonorous note, and the conclusion was reached that the mass represented the stomach, distended greatly by some duodenal obstruction. A barium sulfate meal showed slow evacuation at the pyloric orifice with distention of the descending portion of the duodenum. Four days later there was improvement, permitting the patient to rest in ventral decubitus. Further roentgen studies showed stasis in the submesocolic portion of the duodenum.

A new crisis was immediately relieved by placing the patient in the knee-chest position.

AMESSE, Denver.

INTERMITTENT VOMITING FOLLOWING CONSTRICTION OF THE DUODENUM BY THE MESENTERIC PEDICLE. JEAN LEVESQUE and R. PERROT, Bull. Soc. pédiat. de Paris **37**:587, 1940.

On Sept. 9, 1940, an infant of 19 months was admitted to the hospital with a history of periodic crises of vomiting since the age of 1 year. Up to this time, although there had been minor attacks of vomiting, the baby had developed normally. Suddenly in March 1940 a violent attack of vomiting occurred, which continued for five hours, the general condition becoming alarming. The vomitus contained much bile throughout this entire period.

On May 23, during the military exodus from the district, the infant sustained an attack of bronchopneumonia, which resulted in great emaciation; it was followed immediately by new crises of vomiting, which persisted intermittently until September. One of these attacks lasted for ten days. Roentgenograms revealed an obstruction in the third portion of the duodenum, obviously due to pinching of this organ by the pedicle of the mesentery. On examination in the prone position, however, the obstruction was promptly overcome; the duodenum was uniformly opened, antiperistalsis disappeared and the gastrointestinal route was fully restored. As the patient had always been constipated, a barium sulfate enema was given and a spasm of the colon demonstrated. The treatment of this unusual condition consisted of offering a normal diet for the age and after each meal placing the child in either the ventral or the knee-chest position. Belladonna was prescribed and daily enemas employed. Satisfactory results were noted, the patient gaining promptly and remaining free of vomiting.

AMESSE, Denver.

BRACHYMEGAESOPHAGUS WITH GASTRIC DISPLACEMENT. RIBADEAU-DUMAS, CHABRUN and WALTHER, Bull. Soc. pédiat. de Paris **37**:605, 1940.

A baby of 5 weeks was admitted for vomiting and loss of weight. Attacks of vomiting had begun on the eighth day after birth and followed each feeding, the infant being breast fed. In some instances there was much mucus mixed with curdled milk. The patient had lost 600 Gm., and on examination its weight was 340 Gm. less than its birth weight. Aside from this, however, the infant appeared normal; the appetite was good, and the stools were of proper consistency. Roentgen studies were made of the mediastinum and the gastrointestinal tract. A piriform shadow was found in the right pulmonary field, extending from the body of the

second to the body of the eleventh dorsal vertebra, where it merged with the shadow of the liver. A barium sulfate meal revealed the exact character of the developmental anomaly; the pocket represented in the first roentgenogram was filled readily, and the barium ingested occupied two thirds of the surface of the right hemithorax. The contours of the mass were characterized by peristaltic waves. From this large pocket extended a narrow segment leading into an inferior basin, which, in turn, drained into the small intestine through a long and small canal penetrating the diaphragm. There was no shadow which could be interpreted as representing the stomach within the abdominal cavity. The esophagus was found extremely short and voluminous. The baby was examined one year later and found in excellent health.

AMESSE, Denver.

ALIMENTARY INTOLERANCE SIMULATING A SUBACUTE INFECTION. M. P. MARTROU, Bull. Soc. pédiat. de Paris **37**:620, 1940.

A boy of 18 months was admitted to the hospital with a history of irregular fever for the preceding seven months and a gradual lowering of vitality. The initial symptoms indicated congestion of the right lung. This was followed by otitis, but the fever continued after the latter complication was relieved. Examination of the blood and urine revealed no abnormalities; reactions to tuberculin were negative. Roentgenograms were inconclusive. Treatment with sulfarsphenamine was followed by a gain in weight, but the temperature remained elevated. At this time the infant was pale and edematous, with visible signs of pain and great weakness. He could not speak or walk, and his weight had been reduced to 11 Kg. The diet had consisted entirely of milk during this long illness. It was decided to eliminate milk entirely and offer a general and generous diet. Immediately the temperature fell to normal, and the entire aspect of the patient changed. After eight days of apyrexia a few drops of milk was added, and the response was startling; the fever returned. Again this experiment was tried, with the same result. Meats, eggs, fish and vegetables were well tolerated. Desensitization was attempted but was unsuccessful. The difficulty in clarifying the diagnosis rested on the perfect tolerance for milk during the first year of life and the subsequent toxic reaction. AMESSE, Denver.

PRIORITY OF DOMENICO BATTINI IN DESCRIPTION OF CONGENITAL MEGACOLON DESCRIBED AS HIRSCHSPRUNG'S DISEASE (1888). ALFREDO GIANNINI, Atti e Mem. Accad. Stor. Arte Sanit. **5**:228, 1939.

On the basis of proofs found in careful research, the author comes to the conclusion that the so-called Hirschsprung's disease described in detail in 1888 had been described eighty-eight years previously by D. Battini, and that for this reason it should be called "Battini's disease."

[MITT. Z. GESCH. D. MED. U. NATURWISS.]

A NEW TEST FOR HEPATIC INSUFFICIENCY. A. CASTELLANOS and J. B. NUÑEZ, Bol. Soc. cubana de pediat. **13**:382 (Aug.) 1941.

The authors suggest a new test for hepatic function which is based on the capability of the liver to fix intravenously injected carotene. Two-tenths milligram of carotene per kilogram of body weight is injected intravenously. Blood is taken before the injection and five minutes after the injection. Under normal conditions there should be no elevation of carotene in the blood within five minutes after the injection. Any increase is pathologic and indicates dysfunction of the liver.

SCHLUTZ, Chicago.

VIRUS HEPATITIS: A CONTRIBUTION TO THE KNOWLEDGE OF THE CLINICAL PICTURE OF POLIOMYELITIS AND ENCEPHALITIS. U. STECHELE, Ztschr. f. Kinderh. **62**:504 (April 24) 1941.

The hepatomegaly observed in a considerable number of patients with poliomyelitis or encephalitis should be regarded as being due to the virus. The same virus may cause damage to the liver in one person and involve the central nervous system in another. In a village 6 children and a physician became ill with hepatitis. Eight days later the physician's child was stricken with encephalitis. The author relates that Duken observed 2 pairs of siblings in each of which 1 child had encephalitis and the other hepatitis.

SIEMSEN, Kalamazoo, Mich.

TWO CASES OF COLON POLYPS. S. RUDBERG, Nord. med. (Hygiea) **9**:524 (Feb. 15) 1941.

The first patient was a girl 9 years of age. When she was 2 years old a rectal polypus was seen. Thereafter there was a tendency to bleeding. Six months later the polypus was

extirpated. As the bleeding continued and the rectoscopic examination showed no abnormal condition, a roentgen examination was performed. This disclosed a pendulated polypus in the sigmoid flexure of the colon. This was extirpated by laparotomy when the girl was 8 years old. She was discharged as healthy, and reexamination one year later disclosed no morbid symptoms. The polypus was a fibroadenoma.

A girl of 3½ years had suffered from anal bleeding. Anal fissure was diagnosed at 1 year and again at 3 years of age, and forced dilations were performed. Six months after the last treatment a solitary polypus was demonstrated roentgenologically in the lower part of the descending colon. As the symptoms were very slight, operative treatment was postponed.

WALLGREN, Göteborg, Sweden.

VOLVULUS IN A NEWBORN INFANT. S. RUDBERG, Nord. med. (Hygiea) **9**:527 (Feb. 15) 1941.

A full term infant girl displayed first bilirubin-colored vomitus and later fecal vomiting from the second day of life. Roentgenologically a stenosis of the upper part of the duodenum was demonstrated. Laparotomy on the sixth day showed volvulus of the small intestine at the duodenojejunal flexure. The child died. WALLGREN, Göteborg, Sweden.

SURGICAL TREATMENT OF TEN PATIENTS WITH CONGENITAL MEGACOLON. JAMES HINDMARSH, Nord. med. (Hygiea) **10**:1183 (April 12) 1941.

This is a report of 10 cases of severe megacolon (Hirschsprung's disease) in children who after rather intense preoperative care in the hospital were treated with resection of the left sympathetic trunk corresponding to the second to the fourth lumbar ganglion. In addition, the plexus hypogastricus superior was removed in 2 of the cases in which the megacolon was complicated with urinary incontinence. One of the children died shortly after the operation with capillary bronchitis. The others survived. In 6 cases the result was excellent and the children were regarded as free from symptoms. Three other children were getting better at the time of the report but still suffered from constipation and needed artificial evacuations. Three of the healthy children showed roentgenologically a normal colon after the operation.

WALLGREN, Göteborg, Sweden.

LATE RESULTS OF OPERATION FOR CONGENITAL PYLORIC STENOSIS. S. NYBORG, Nord. med. **10**:1190 (April 12) 1941.

This is a short report on 8 cases of pyloric stenosis in which operation was performed after the method of Ramstedt and roentgen reexamination was made one and a half to eight years later. Two of the children were normal (5 and 8 years of age); the other children showed more or less remaining roentgenologic changes, as described by Runström.

WALLGREN, Göteborg, Sweden.

MEGACOLON AND ITS TREATMENT WITH SYMPATHECTOMY. MARTI HÄMÄLÄINEN, Nord. med. (Finska läk.-sällsk. handl.) **10**:1312 (April 26) 1941.

Nine children with signs and symptoms of megacolon since the first year of life were operated on. A subperitoneal bilateral resection of the splanchnic nerves combined with a resection of the superior lumbar ganglions was performed. In 7 cases the result was excellent; in 1 case there was no therapeutic effect, and in the last case the splanchnic nerves could not be found at the operation.

WALLGREN, Göteborg, Sweden.

THREE CASES OF RELAXATIO DIAPHRAGMATICA. WILLY MATHIESEN, Nord. med. **11**:2140 (July 12) 1941.

One of the patients was a boy of 7 months who began to display slight dyspnea after eating. The heart was displaced to the right and there was a tympanitic percussion sound over the lung, which changed to dulness after feeding, with impaired respiration. Roentgenologically the vertex of the diaphragm was found at the fourth rib and the contour of the muscles was smoothly arched and distinctly separated from the stomach.

WALLGREN, Göteborg, Sweden.

CASE OF CHOLEDOCHUS CYST. L. HOLMBERG, Nord. med. **11**:2706 (Sept. 20) 1941.

The patient was a girl of 8 years who had had epigastric pains and frequent vomiting since she was about 1 year old. During observation at a hospital she was found icteric.

This was thought to be due to acute hepatitis; but it remained for several months, and there was no filling of the gallbladder shown on the cholecystogram. Later the jaundice became intermittent and eventually extreme, with acholic stools. A rounded tumor was felt at the umbilicus. At the operation a choledochus cyst was found. After cystoduodenostomy the girl recovered and was discharged healthy.

WALLGREN, Göteborg, Sweden.

BIOPSY OF THE LIVER IN CASES WITH INTERMITTENT JUVENILE JAUNDICE. NIELS B. KRARUP and POUL IVERSEN, Ugesk. f. læger **103**:72 (Jan. 16) 1941.

Krarup and Iversen report on 5 cases of benign intermittent jaundice without bilirubinuria in young people. Biopsy in 3 cases showed a normal histologic picture of the liver; in 2 cases, moderate fatty infiltration. The jaundice is considered to be due to dysfunction of the liver.

WALLGREN, Göteborg, Sweden.

Diseases of the Ductless Glands; Endocrinology

A CASE OF ADDISON'S DISEASE. ARVID WALLGREN, Swenska läk.-tidning. **38**:379 (Feb. 14) 1941.

The author reports a case of Addison's disease in a 14 year old boy. The illness developed after an influenza-like disease. Fatigue, loss of appetite, pigmentation of the skin, vomiting, polydipsia, polyuria and hypostenuria were the outstanding features. The blood pressure was 90 systolic and 60 diastolic. The nonprotein nitrogen content of the blood was increased, to 58.2 mg. per hundred cubic centimeters. His Wassermann reaction and his reaction to tuberculin were negative. He made rapid improvement with large doses of sodium chloride and desoxycorticosterone. With this treatment the boy was able to continue in school for a year and a half, when a rapid change for the worse set in. The progress of the disease could not be stopped by intravenous injections of desoxycorticosterone. At necropsy both adrenal glands were found to be severely atrophic, but no other morbid changes were revealed.

WALLGREN, Göteborg, Sweden.

A CASE OF HYPERTHYROIDISM. GERT VON SYDOW, Swenska läk.-tidning. **38**:386 (Feb. 14) 1941.

The author reports the case of a 10 year old girl with mild struma, tachycardia, irritability and various nervous symptoms. The basal metabolic rate was 100 per cent. There was no exophthalmos and no sweating. Improvement was brought about by small doses of iodine, rest in bed and restorative treatment.

WALLGREN, Göteborg, Sweden.

ENLARGEMENT OF THE LIVER IN DIABETIC CHILDREN. NIELS B. KRARUP and POUL IVERSEN, Ugesk. f. læger **103**:63 (Jan. 16) 1941.

This is a report of 2 cases of severe juvenile diabetes with pronounced hepatomegaly. Biopsy showed that the enlargement was due principally to edematous choking of the liver cells, partly to slight fatty infiltration. The glycogen content was normal. After careful regulation of the diet and insulin treatment the hepatomegaly disappeared.

WALLGREN, Göteborg, Sweden.

RELATION BETWEEN THYROID FUNCTION AND THE CHOLESTEROL CONTENT OF THE BLOOD OF INFATS AND LARGER CHILDREN. GRETE GØRTZ, Ugesk. f. læger **103**:181 (Feb. 6) 1941.

In 3 cases of hypothyroidism in children less than 2 years of age no hypercholesteremia was demonstrable. It is suggested that during the first six months of life there is a hypocholesteremia in myxedematous infants.

WALLGREN, Göteborg, Sweden.

Diseases of the Muscles, Bones, Joints and Lymph Glands

VARIATIONS IN THE CALCIFICATION PATTERN IN EPIPHYSES: THEIR NATURE AND SIGNIFICANCE. LESTER WARREN SONTAG and S. IDELL PYLE, Am. J. Roentgenol. **45**:50 (Jan.) 1941.

Serial roentgenograms of a series of 220 children are reviewed. The variation in calcification pattern is best observed and is most consistent in the distal femoral epiphysis. This

consists of marked roughening, with frequent loss of regular outline, and occasionally calcified particles are found beyond the border proper of the epiphysis. It occurred to some degree in every child of the group, usually at 12 to 18 months. It was always bilateral and asymptomatic and should not be mistaken for an epiphysitis; it occurred earlier in girls and in children with rapid skeletal growth, who started walking earlier. There is believed to be a definite relation between the time of appearance and hyperthyroidism or hypothyroidism. It is believed this occurs more consistently in this epiphysis owing to its more rapid and lateral development, with consequent irregularity of proliferating cartilage. SQUIRE, Chicago.

Diseases of the Eye

TRACHOMA AND SULFANILAMIDE. J. L. PAVIA, Arch. de oftal. de Buenos Aires **15**:400 (Aug.) 1940.

This paper gives an account of the work of the Argentine Committee for the Prevention of Blindness and War Against Trachoma in connection with the latter issue. The committee localized trachoma in different areas, classifying it into different types according to MacCallan.

The following dosage was used when sulfanilamide was employed: 0.04 Gm. per kilogram of body weight a day for five days, 0.03 Gm. per kilogram a day for five days and 0.02 Gm. per kilogram a day for five days.

There were no general disturbances; there was a rapid decrease in the complicating inflammations, and the nodules disappeared in fifteen to twenty days, with marked reduction of the pannus.

C. E. FINLAY. [ARCH. OPHTH.]

RETINITIS PUNCTATA ALBESCENS. F. PONCE DE LEON and R. A. MAFFRAND, Arch. de oftal. de Buenos Aires **15**:582 (Nov.) 1940.

Three cases are reported in a single family; there were hemeralopia, contraction of the visual fields and the usual objective lesions. The literature is reviewed, and opinions as to the relations of the disease to retinitis pigmentosa and allied conditions, with the differential diagnosis, are discussed.

C. E. FINLAY. [ARCH. OPHTH.]

CONGENITAL MALFORMATIONS: STRANDS REPLACING BOTH SUPERIOR RECTUS MUSCLES, ABSENCE OF INFERIOR RECTUS MUSCLES, MICROCORNEA AND COLOBOMA OF IRIS; NEW OPERATIVE METHOD TO CORRECT HYPERTROPIA OF EYEBALLS. M. BARTELS, Klin. Monatsbl. f. Augenh. **104**:727 (June) 1940.

A woman aged 32 could not move her eyes upward or downward. The pupils were hidden beneath the upper lids. The condition grew worse with advancing age, although no operation for ptosis had been performed. Bartels used a new method of operating on the two eyes, at two sittings, six days apart. After the conjunctiva was incised horizontally at the site of the insertion of the superior rectus muscle, the strand replacing it was excised as far back as possible. The conjunctiva was united in a perpendicular direction, the conjunctiva thus being lengthened. Then a horizontal incision was made through the conjunctiva over the insertion of the inferior rectus muscle, no trace of which was found, not even far back. A large crescent-shaped piece of conjunctiva was removed from the lower tip of the wound, which was closed horizontally. A double-armed guide suture was laid through the conjunctiva and the episclera at the lower limbus, through the lower fornix and through the skin, where it was fastened over a rubber tube, the eyeball thus being pulled downward. A low degree of diplopia disappeared soon after the operation, and slight motion upward and downward was noted. This effect was due to the function of the inferior oblique muscles in the author's opinion. The accompanying bilateral microcornea and coloboma of the iris are proof that macular malformations need not be of central origin but may have a peripheral genesis.

K. L. STOLL. [ARCH. OPHTH.]

MULTILAMELLAR CATARACT WITH GLOBULES: REPORT OF A CASE. M. BÜCKLERS, Klin. Monatsbl. f. Augenh. **105**:312 (Sept.) 1940.

Bücklers reports on a girl aged 6 years whose family history showed no consanguinity, no rickets and no tetany. The parents noticed that the pupils turned gray while the child had measles when 3 years old. Four layers could be noted in the lens, and diffusely reflecting spheroids were formed in the second and third layers. A number of round pearls were

observed at the equator of the inner layer and smaller ones of a similar type on the anterior surface of the outer layer. Such pearls were observed by Axenfeld and Stock in cataracta zonularis. The larger pearls found at the equator occur rarely. They consist of calcium phosphate (Wessely). This rare type of concentric layers in lamellar cataract was observed in hereditary cataracta pulverulenta. The dotted opacities, however, were finer, dust shaped and more closely packed in Bücklers' case than in cataracta pulverulenta. The cortex was barely cloudy between the opaque shells. The described formation may have developed prior to or after birth. It is uncertain whether this cataract was of an endogenous or exogenous nature or was caused by determinative or chemiconutritive influences.

K. L. Stoll. [Arch. Ophth.]

Skin Diseases; Allergy

Familial Occurrence of Pruritus, Urticaria and Paresthesias with Hyperkinesis of the Lower Extremities. J. C. Mussio-Fournier and F. Rawak, Confinia neurol. **3**:110, 1940.

Mussio-Fournier and Rawak describe a syndrome found in 3 members of one family. The clinical manifestations were pruritus, urticaria and hyperkinesis of the lower extremities caused by paresthesias appearing during rest. While other members of the same family also showed allergic reactions, the authors express the belief that the present symptoms were not specifically allergic but were secondary to heredodegeneration of the nervous system.

De Jong, Ann Arbor, Mich. [Arch. Neurol. & Psychiat.]

Miscellaneous

Congenital Diaphragmatic Hernia (Right Side). Stayitch and Stoyanovitch, Bull. Soc. pédiat. de Paris **37**:526, 1940.

A girl of 3½ years was admitted to the hospital on Jan. 16, 1939 with bronchopneumonia affecting the right side; one month previously she had suffered from an attack of grip with severe and continuous cough. Examination showed a pale child, emaciated and dyspneic, with a temperature of 38.5 C. (101.3 F.) and a pulse rate of 110. Percussion of the chest revealed dulness from the spine of the scapula to the base of the lung on the right side, while auscultation showed diminished respiration with a few subcrepitant rales in this area, with sonorous rales on the left side. The abdomen was entirely normal. Two days later dulness over the right side was complete and roentgenograms demonstrated the presence of a multilobular shadow in the right hemithorax. Examination also revealed gurgling noises, obviously intestinal, in the right side of the chest. On January 25 the acute pulmonary process had subsided. The patient was unable to swallow a barium sulfate meal, so a barium sulfate enema was given, and roentgenologic studies were continued. The lower part of the bowel filled normally up to the right portion of the transverse colon, which had invaded the chest, and the barium showed clearly at the level of the fourth rib. From this point the colon descended to the cecum, which was pulled up to the highest part of the right iliac fossa. A diagnosis of diaphragmatic hernia (right side) with an orifice antehepatic and retrosternal was made. The condition of this patient improved so rapidly that surgical intervention was not carried out, and she was dismissed with instructions to return for periodic examination.

Amesse, Denver.

Dwarfism and Diabetes Insipidus with Congenital Lesion of the Biliary Tract in a Child of Six Years. H. Grenet, R. Levent and P. Isaac-Georges, Bull. Soc. pédiat. de Paris **37**:538, 1940.

A boy of 6 years, was brought to the clinic in a deplorable state. His weight was that of a child of 2 years; the skin had a grayish hue; the eyes were sunken, and there was a subicteric tinge to the conjunctivas. Emaciation was extreme, but the abdomen was distended by the enormous enlargement of the liver, which was found to be hard and insensitive. The child was weak; he tired easily and was unable to play. The most striking point in the examination, however, was the boy's stature, being only 89 cm., the usual height of a boy of 3 years. In addition to the enlarged liver, the spleen was palpable for 4 cm. below the costal arch, but there was no ascites or adenopathy.

The patient complained of intense thirst; he drank 2 or 3 liters of liquids daily and excreted equal amounts of urine. The specific gravity was 1.002 and the urea content 55 mg. per hundred cubic centimeters. The urine contained no sugar, albumin, acetone, blood or casts.

The Wassermann reaction was negative, and roentgenograms of the bony structure revealed nothing of interest. A biopsy of the liver was made, and a congenital malformation of the intrahepatic bile ducts was demonstrated. Treatment with an extract of posterior lobe of the hypophysis and with liver extract was futile, and the prognosis remained as cloudy after twenty-two months of management as at the time of admission. AMESSE, Denver.

SEVERE TYPE OF HEATSTROKE IN INFANCY. ANDRÉ FULCONIS, Bull. Soc. pédiat. de Paris **37**:610, 1940.

An infant of 2½ months with a history of digestive disturbances, probably brought on by irregular feeding in a poorly managed nursery, was found at the foot of its crib with the bed clothing wrapped tightly about the head and body, prostrated by heat and partially asphyxiated. The temperature was 40 C. (104 F.); the skin was cyanosed, and the patient was in coma, with pulse and respiration hardly perceptible, the eyes sunken and the fontanel depressed. With oxygen and caffeine promptly administered, the immediate urgency was relieved, but a short time later there were dyspnea, fever and tachycardia with alternate pallor and congestion and suppression of urine. Eight hours after the accident, vomiting and diarrhea were noted; this aggravated the existing dehydration. On the following morning, symptoms referable to the nervous system were added. Phleboclysis was begun on the second day, replacing subcutaneous injections of solutions of dextrose, and was continued for three and one-half days, when the infant was manifestly safe and use of a formula of dry milk was resumed. Recovery was complete within a few days thereafter. AMESSE, Denver.

News and Comment

GENERAL NEWS

American Board of Pediatrics.—The dates for the fall examinations have been set. Written examinations will be held locally, under a monitor, on Oct. 8, 1943, and an oral examination, in New York, on November 20 or 21. Further information regarding these examinations may be procured from the secretary, Dr. C. A. Aldrich, Children's Memorial Hospital, 700 Fullerton Avenue, Chicago.

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after the examinations in St. Louis on March 27 and 28, 1943: Egbert Vernon Anderson, Pensacola, Fla. (in the Navy); Henry L. Barnett, St. Louis; Lester Edward Bower, Chicago; Joseph Alfred Carbone, Gary, Ind. (in the Army); John Henry Doval, St. Louis; C. Hall Farmer, Macon, Ga.; Anita Edith Faverman, San Francisco; Alexander N. Freed, Cleveland (in the Army); Morton J. Freedman, Peoria, Ill. (in the Army); Lawrence Eddy Goldman, St. Louis; Charles F. Good, Cleveland (in the Army); Salmon Reclus Halpern, Dallas, Texas (in the Army); Martin J. Harris, Louisville, Ky. (in the Army); Alex Klinkowstein, Detroit (in the Army); W. Wayne Lockwood, Urbana, Ill. (in the Navy); Harold D. Lynch, Evansville, Ind.; Ruben Meyer, Detroit; William G. Motel, Chicago (formerly Springfield, Ill.); Charles Eugene Muhleman, LaPorte, Ind. (in the Army); Wesley Stephan Nock, Chicago (in the Navy); L. Paul Rasmussen, Salt Lake City, Utah; Edith C. Robinson, St. Louis; Margaret Mary Scannell, Indianola, Miss.; Lloyd M. Simonson, Sheboygan, Wis.; Harry H. Slemens, Marysville, Calif.; Eugene A. Stack, Chicago (in the Navy); George Ewing Stafford, Salina, Kan. (in the Army); C. S. E. Touzel, Fort Worth, Texas; Robert A. Trombley, Albuquerque, N. Mex. (in the Navy); Ly Werner, Albuquerque, N. Mex.; Thelma Marie Wygant, Detroit; Melvin Francis Yeip, Cleveland (in the Navy).

The following were certified after the examinations in New York on April 23 and 24, 1943: Hattie E. Alexander, New York; George King Anderson, Washington, D. C.; Katherine Bain, Washington, D. C.; Edward E. Brown, Elmhurst, N. Y.; Eliza Hunton Caldwell, Pelham, N. Y.; Hugh A. Carithers Jr., Jacksonville, Fla. (in the Army); Merl John Carson, Raleigh, N. C.; J. Frederick Close, Greenwich, Conn.; Samuel Dillon, Rockaway Park, N. Y.; Frank A. Disney, Rochester, N. Y.; Raymond George Filsinger, Buffalo; Nathan Michael Greenstein, New York (in the Navy); Alexander D. Gross, Queens Village, N. Y.; Edward Adams Hardy, Pelham, N. Y. (in the Army); Frederic Sargent Huntington, Darien, Conn.; Roswell Dorr Johnson, New Haven, Conn.; Nathan Robert Kahn, Brooklyn (in the Army); Arthur A. Kaplan, Utica, N. Y. (in the Army); Ruskin King, Savannah, Ga.; William Howell Kiser Jr., Atlanta, Ga.; Isidore Leber, Brooklyn (in the Army); Ethel Margaret MacLean, Farmington, Conn.; Israel J. May, Brooklyn; Emerson K. McVey, Chicago (in the Army); David Merksamer, Brooklyn; Edward S. O'Keefe, Lynn, Mass.; George Edward Oosterhous, Madison, Wis. (in the Army); Irving B. Richter, Chicago (in the Army); Meinhard Robinow, Augusta, Ga.; Frederick Peckham Rogers, West Hartford, Conn. (in the Army); Lewis J. Schloss, New York (in the Army); Jacob J. Schneider, Brooklyn; Annie V. Scott, New York; Benjamin Stein, Washington, D. C.; Daniel Michael Tolmach, Wester Haverstraw, N. Y.; Ethel H. Trygstad, Central Islip, N. Y.; Edward V. Turner, Wilmington, N. C.; Elizabeth Ufford, Port Washington, N. Y.; Rudolph E. Vandeveer, Rome, N. Y.; Martha Cook Wager, New York; Frank Strattan White, Teaneck, N. J. (in the Navy); Gladys Claire Winter, Teaneck, N. J.

The total number of specialists certified by the American Board of Pediatrics is brought to 2,130. This includes the deceased specialists.

Book Reviews

The Function of the Orgasm. By Wilhelm Reich, M.D. Price, $3.00. Pp. 368, with 48 illustrations. New York: Orgone Institute Press, Inc., 1942.

This is a difficult book to review. Any attempt to close the gap between physical and mental causes and effects gets into the field of emotion. Words are still inadequate to bridge this gap. The author accepts the responsibility of making a new approach to the problem of mental disease. He says his book is concerned with "revolutionary knowledge." Many statements are made with the assurance of one in revolt, but too many of them are based on other statements whose power to convince lies entirely in the force of the words used.

Reich states that this is a narrative rather than a textbook. The first three chapters give an account of how he came to his belief in the orgasm theory. There are many statements in italics, many with new terms. Some are defined, but some of the definitions are sources of further confusion. He states that sex economy has become a new branch of science, defined as "that body of knowledge which deals with the economy of the biological energy of the organism, with its energy-household." In a book seeking specificity, inadequacy of definition is distressing.

The author appreciates Freud's work in insisting on the place of sexual life of man in the cause and content of mental disorders. He would explain Freud's "Unconscious" in terms of "vegetative impulses and bodily sensations." In his attempts to correlate psychogenic and somatogenic, he goes little beyond the statement, "A psychic experience may produce a lasting alteration in an organ," citing a case in which muscular atrophy occurred. He uses the term "vegetative" in a number of instances, and apparently "vegetative" supplies a meeting ground for mind and body. The orgasm in its creative role deserves the vegetative quality of the fundamental.

Disturbance of orgastic potency is the specific cause of disturbance of sexuality in general. Influence of the purpose or goal on the factors that build up to that goal is well set forth. Orgastic adequacy is Reich's solution of the oedipus complex. Such adequacy is attained through the processes of "sex-economy" and "vegetotherapy."

To put the theory on a scientific basis, the author builds up his premise—the conflict between two things easily spoken of but almost indefinable: (1) the strength of the pleasure of the orgasm and (2) the attitude of society toward recognition of this strength. Then he attempts to diagram the act of orgasm: Erection and mechanical tension lead to electrical charge, which leads to electrical discharge, which leads to loss of erection and mechanical relaxation.

The surrender of voluntary muscular activity, or orgasm reflex, is illustrated with a case history. The patient acted out situations and attitudes of earlier life, even back to infantile sucking. As the significance of these activities brought the related mental attitudes up to consciousness, he was cured of his compulsive drinking, and humility ensued!

"Orgastic impotence and anxiety create sympatheticotonia." The basic characteristic of such sympatheticotonia is the "chronic inspiratory attitude of the thorax and the limitation of full expiration." This statement is made after a description of the observations the author has made of patients whose ability to exhale seemed to him faulty. Apparently, the observations of respiration have to do with the "vegetative" level, and disturbances of respiration are related to disturbances of reflex muscular activity, especially such as occur in the orgasm reflex.

There are a few pages on psychosomatic diseases. Perhaps it is impossible to be wise in one's thinking here, but statements are made that seem too futile even in this field.

In the last twenty pages, the author attempts to put his theory on a scientific basis. Bioelectrical phenomena are demonstrated with appropriate instruments. They are held to show the reality and validity of energy changes commensurate with orgastic adequacy. Charge and discharge (electrical) are made to equal tension and relaxation, which equal preorgasm and postorgasm. Finally, the energy demonstrated electrically is termed bioelectrical and is ascribed to bions of orgone energy.

The book is provocative, but confusing rather than convincing.